

CONSUMPTION OF ALCOHOLIC BEVERAGES

Consumption of alcoholic beverages was considered by previous IARC Working Groups in 1987 and 2007 ([IARC, 1988, 2010](#)). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Types and ethanol content of alcoholic beverages

1.1.1 Types of alcoholic beverages

The predominant types of commercially produced alcoholic beverages are beer, wine and spirits. Basic ingredients for beer are malted barley, water, hops and yeast. Wheat may be used. Nearly all wine is produced from grapes, although wine can be also made from other fruits and berries. Spirits are frequently produced from cereals (e.g. corn, wheat), beet or molasses, grapes or other fruits, cane sugar or potatoes. Main beverage types (i.e. beer, wine and spirits) may be consumed in combination with each other to fortify the strength of an alcoholic beverage (e.g. fortified wine, in which spirits are added to wine) ([WHO, 2004](#)).

In addition to commercialized products, in many developing countries different types of home- or locally produced alcoholic beverages such as sorghum beer, palm wine or sugarcane spirits are consumed ([WHO, 2004](#)). Home- or locally produced alcoholic beverages are produced through fermentation of seed, grains,

fruit, vegetables or parts of palm trees, by a fairly simple production process.

1.1.2 Ethanol content of alcoholic beverages

Percentage by volume (% vol) is used to indicate the ethanol content of beverages, which is also called the French or Gay-Lussac system. Alcohol content differs according to the main beverage type and may also vary by country. Commonly, 4–5% vol are contained in beer, about 12% vol in wine and about 40% vol in distilled spirits. However, lower or higher ethanol content in alcoholic beverages is also possible. The ethanol content in beer can range from 2.3% vol to over 10% vol (lower alcohol content in home- or locally produced alcoholic beverages such as sorghum beer), in wine from 8 to 15% vol, and in spirits from 20% vol (aperitifs) to well over 40% vol (e.g. 80% vol in some kinds of absinthe). There is a trend in recent years towards higher (13.5–14.5%) alcohol volume in consumed wines, associated with technology advances and increasing proportion in overall consumption of wines produced outside the traditional wine-growing regions of Europe ([IARC, 2010](#)).

To calculate the amount of ethanol contained in a specific drink, the amount (e.g. ml) of

alcoholic beverage consumed for each type of beverage (e.g. a 330-mL bottle of beer) is multiplied by the percentage of alcohol by volume, i.e. the proportion of the total volume of the beverage that is alcohol (e.g. $(330 \text{ mL}) \times (0.04) = 13.2 \text{ mL}$ of ethanol in a bottle of beer). Conversion factors may be used to convert the volume of alcoholic beverage into grams of ethanol, or volumes of alcohol may be recorded in ‘ounces’. Conversion factors for these different measures ([WHO, 2000](#)) are as follows:

- 1 mL ethanol = 0.79 g
- 1 UK oz = 2.84 cL = 28.4 mL = 22.3 g
- 1 US fluid oz = 2.96 cL = 29.6 mL = 23.2 g

1.2 Chemical composition

The main components of most alcoholic beverages are ethanol and water. Some physical and chemical characteristics of anhydrous ethanol are as follows ([O’Neil, 2001](#)):

Chem. Abstr. Services Reg. No.: 64–17.5

Formula: $\text{C}_2\text{H}_5\text{OH}$

Relative molecular mass: 46.07

Synonyms and trade name: Ethanol, ethyl alcohol, ethyl hydroxide, ethyl hydrate, absolute alcohol, anhydrous alcohol, dehydrated alcohol

Description: Clear, colourless, very mobile, flammable liquid, pleasant odour, burning taste

Melting-point: $-114.1 \text{ }^\circ\text{C}$

Boiling-point: $78.5 \text{ }^\circ\text{C}$

Density: $d_4^{20} 0.789$

Refractive index: $n_D^{20} 1.361$

In addition to ethanol and water, wine, beer and spirits contain volatile and non-volatile compounds. Volatile compounds include aliphatic carbonyl compounds, alcohols, monocarboxylic acids and their esters, nitrogen- and sulfur-containing compounds, hydrocarbons, terpenic compounds, and heterocyclic and aromatic compounds. Non-volatile extracts of alcoholic beverages comprise unfermented

sugars, di- and tribasic carboxylic acids, colouring substances, tannic and polyphenolic substances and inorganic salts ([IARC, 2010](#)).

Occasionally, toxic additives, that are not permitted for use in commercial production have been identified in alcoholic beverages. These include methanol, diethylene glycol (used as sweetener) and chloroacetic acid or its bromine analogue, sodium azide and salicylic acid, which are used as fungicides or bactericides ([Ough, 1987](#)).

Contaminants may also be present in alcoholic beverages. Contaminants are defined as substances that are not intentionally added but are present in alcoholic beverages due to production, manufacture, processing, preparation, treatment, packing, packaging, transport or holding, or as a result of environmental contamination. Contaminants and toxins found in alcoholic beverages are nitrosamines, mycotoxins, ethyl carbamate, pesticides, thermal processing contaminants, benzene, and inorganic contaminants such as lead, cadmium, arsenic, copper, chromium, inorganic anions, and organometals ([IARC, 2010](#)).

In view of the potential carcinogenicity of acetaldehyde and its known toxic properties, recent studies attempted to estimate exposure to acetaldehyde from alcoholic beverages outside ethanol metabolism at known levels of alcohol exposure. The average exposure to acetaldehyde as a result of consumption of alcoholic beverages, including “unrecorded alcohol,” was estimated at $0.112 \text{ mg/kg body weight/day}$ ([Lachenmeier et al., 2009a](#)). Levels of acetaldehyde in alcoholic beverages vary from less than 1 g/hl of pure alcohol up to 600 g/hl , and high concentrations of acetaldehyde were documented in alcoholic beverages commonly consumed in many parts of the world, including distilled beverages from Brazil, the People’s Republic of China, Guatemala, Mexico, and the Russian Federation, as well as calvados and fortified wines and fruit and marc spirits from Europe ([Lachenmeier &](#)

[Sohnius, 2008](#); [Linderborg et al., 2008](#); [Kanteres et al., 2009](#); [Lachenmeier et al., 2009b](#)).

1.3 Trends in consumption of alcoholic beverages

Volume, pattern and quality of consumed alcohol are included in the description of differential exposure to alcohol.

In a development of the WHO Global Alcohol Database, WHO has developed the Global Information System on Alcohol and Health ([WHO, 2008](#)). In 2008–09, WHO conducted the Global Survey on Alcohol and Health, collecting data on alcohol consumption, alcohol-related harm and policy responses from its Member States.

Total adult per capita consumption in litres of pure alcohol is defined as the total amount of alcohol consumed per person, taking into account recorded consumption (i.e. alcoholic beverages consumed that are recorded in official statistics of production, trade or sales) and unrecorded consumption (i.e. alcoholic beverages consumed that are not recorded in official statistics and that can come from a variety of sources such as home- or informally produced alcohol, illegal production and sale, smuggling and cross-border shopping), and subtracting consumption by tourists, if possible. Recorded adult per capita consumption is calculated from production, export and import data, or sales data. Unrecorded consumption is computed from representative surveys, specific empirical investigations or expert opinion. The percentage of lifetime and past-year abstainers provide important information about drinking in a population and complement the indicator on total adult (15+ years) per capita consumption.

Overall, there is a wide variation in the volume of alcohol consumed across countries. As presented in [Table 1.1](#) and [Table 1.2](#) (available at <http://monographs.iarc.fr/ENG/Monographs/>

[vol100E/100E-06-Table1.2.pdf](#)), the countries with the highest overall consumption of alcohol per capita among the adult (15+ years) population can be found in the the WHO Regional Office for European Region (12.2 L of pure alcohol per capita), and more specifically in eastern Europe. The next highest alcohol consumption is in the WHO Region of the Americas (8.7 L of pure alcohol per capita). Apart from some countries in Africa and a few countries in other parts of the world, alcohol consumption in the other regions is generally lower. The WHO Eastern Mediterranean Region ranks lowest with 0.7 litres of alcohol consumed per adult. Total adult (15+ years) per capita consumption in litres of pure alcohol by region and country is an indicator of the alcohol consumption level of the adult population, irrespective of the number of abstainers (i.e. people who do not drink alcohol) in the country.

Globally, men consume more alcohol than women. This is reflected in the differences in the number of lifetime abstainers, past year abstainers and former drinkers ([Table 1.2 on-line](#)). Lifetime abstainers are defined as the proportion of people (15+ years) in a given population who have not consumed any alcohol during their lifetime, assessed at a given point in time. Past year abstainers are people aged 15+ years who did not consume any alcohol during the past year. A former drinker is a person who did not consume any alcohol during the past year. Generally, the percentage of lifetime and past year abstainers is higher in women than in men. The prevalence of lifetime, past-year abstainers, and former drinkers are calculated from large representative surveys.

[Table 1.2 \(on-line\)](#) provides information about the trend (i.e. robust estimate of five-year change) in per capita consumption (2001–05) of recorded alcohol, that is, indicates if consumption remained stable, increased, decreased, or if no conclusion could be drawn. To estimate five-year change in recorded adult (15+ years) per

Table 1.1 Estimate for total adult (15+ years) per capita consumption, by WHO region, average 2003–05

WHO Region	Adult (15+) per capita consumption*, total (recorded and unrecorded), average 2003–05
African Region (AFRO)	6.2
Region of the Americas (AMRO)	8.7
Eastern Mediterranean Region (EMRO)	0.7
European Region (EURO)	12.2
South-East Asian Region (SEARO)	2.2
Western Pacific Region (WPRO)	6.3

* in litres of pure alcohol

Source: [WHO \(2008\)](#)

AFRO: Algeria, Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Rwanda, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, South Africa, Swaziland, Togo, Uganda, United Republic of Tanzania, Zambia, Zimbabwe

AMRO: Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Bolivia, Brazil, Canada, Chile, Colombia, Costa Rica, Cuba, Dominica, Dominican Republic, Ecuador, El Salvador, Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, United States of America, Uruguay, Venezuela (Bolivarian Republic of)

EMRO: Afghanistan, Bahrain, Djibouti, Egypt, Islamic Republic of Iran, Iraq, Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Morocco, Oman, Pakistan, Qatar, Saudi Arabia, Somalia, Sudan, Syrian Arab Republic, Tunisia, United Arab Emirates, Yemen

EURO: Albania, Andorra, Armenia, Austria, Azerbaijan, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Luxembourg, Malta, Monaco, Montenegro, Netherlands, Norway, Poland, Portugal, Republic of the Republic of Moldova, Romania, Russian Federation, San Marino, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Tajikistan, The former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Ukraine, United Kingdom, Uzbekistan

SEARO: Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, Timor-Leste

WPRO: Australia, Brunei Darussalam, Cambodia, China, Cook Islands, Fiji, Japan, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Federated States of Micronesia, Mongolia, Nauru, New Zealand, Niue, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Singapore, Solomon Islands, Tonga, Tuvalu, Vanuatu, Viet Nam

capita consumption, three-year moving averages were calculated for per capita consumption of recorded alcohol for each year in the five-year period from 2001 to 2005.

Recent data on trends in consumption of alcoholic beverages indicate that the European Region and the Region of the Americas maintain a steady high consumption of alcoholic beverages, with 20% of all countries showing an increase in consumption. Alcohol consumption remains low in the Eastern Mediterranean Region. In the African Region, out of 50 countries, 20% show a decrease and 20% an increase in consumption. There is a recent and continuing increase in alcohol consumption in several low and middle-income countries in the South-East

Asia and Western Pacific Regions, which probably reflects economic development and increases in consumers' purchasing power as well as increases in the marketing of branded alcoholic beverages ([WHO, 2007](#)).

2. Cancer in Humans

2.1 Description of cohort studies

2.1.1 Studies in the general population

Cohort studies are classified by the country in which the study was conducted (Table 2.1 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.1.pdf>). The majority of

cohort studies have been conducted in the USA, western Europe and Japan. Since the previous *IARC Monograph* ([IARC, 2010](#)), data on the association between alcohol consumption and risk of cancer have been published from several cohorts, including updates of cohorts described previously ([Bongaerts et al., 2006, 2008](#); [Li et al., 2006, 2009b](#); [Weinstein et al., 2006](#); [Ericson et al., 2007](#); [Ferrari et al., 2007](#); [Ishihara et al., 2007](#); [Ozasa, 2007](#); [Sutcliffe et al., 2007](#); [Thygesen et al., 2007, 2008a, b](#); [Fan et al., 2008](#); [Ide et al., 2008](#); [Kabat et al., 2008](#); [Nielsen & Grønbaek, 2008](#); [Rohrmann et al., 2008, 2009](#); [Shimazu et al., 2008](#); [Friberg & Wolk, 2009](#); [Ishiguro et al., 2009](#); [Heinen et al., 2009](#); [Klatsky et al., 2009](#); [Rod et al., 2009](#); [Thun et al., 2009](#); [Weikert et al., 2009](#)) and reports from recently established cohorts and some older cohorts from which data on alcohol consumption and risk of cancer were not available ([Nakaya et al., 2005](#); [Velicer et al., 2006](#); [Akhter et al., 2007](#); [Chlebowski et al., 2007](#); [Freedman et al., 2007a, b](#); [Friborg et al., 2007](#); [Gwack et al., 2007](#); [Khurana et al., 2007](#); [Lim et al., 2007](#); [Mørch et al., 2007](#); [Sung et al., 2007](#); [Tsong et al., 2007](#); [Visvanathan et al., 2007](#); [Zhang et al., 2007a](#); [Ansems et al., 2008](#); [Brinton et al., 2008, 2009](#); [Chao et al., 2008](#); [Lim & Park, 2008](#); [Muwonge et al., 2008](#); [Ohishi et al., 2008](#); [Toriola et al., 2008, 2009](#); [Allen et al., 2009](#); [Duffy et al., 2009](#); [Engeset et al., 2009](#); [Gibson et al., 2009](#); [Gong et al., 2009](#); [Jiao et al., 2009](#); [Johansen et al., 2009](#); [Lew et al., 2009](#); [Setiawan et al., 2009](#); [Chao et al., 2010](#)).

2.1.2 Studies in special populations

This group of studies is characterized by the assumption that the study subjects have a pattern of consumption of alcoholic beverages that is different from that of the general population, e.g. alcoholics, brewery workers, members of a temperance organization (Table 2.2 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.2.pdf>). Because of the

availability of national registries of populations, inpatients and cancer, these studies were largely performed in Scandinavian countries. The estimation of risk in these individuals is not based upon a comparison of exposed and unexposed subjects within the cohort, but with the expected rates of cancer in the general population. [Thygesen et al. \(2009\)](#) is the only report from cohorts of special populations that has been published since [IARC \(2010\)](#).

2.2. Cancers of the upper aerodigestive tract

2.2.1. Cancer of the oral cavity and pharynx

It was concluded in the previous *IARC Monograph* ([IARC, 2010](#)) that consumption of alcoholic beverages is causally related to cancer of the oral cavity and pharynx, and that the risk increases in a dose-dependent manner.

(a) Overview of cohort and case-control studies

The association of consumption of alcoholic beverages and risk of cancer of the oral cavity and/or pharynx has been assessed in six cohort studies ([Freedman et al., 2007a](#); [Friborg et al., 2007](#); [Ide et al., 2008](#); [Muwonge et al., 2008](#); [Allen et al., 2009](#); [Weikert et al., 2009](#); Table 2.3 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.3.pdf>). Significant increases in risk were found with increasing amount of alcohol consumption in all studies ([Freedman et al., 2007a](#); [Friborg et al., 2007](#); [Ide et al., 2008](#); [Allen et al., 2009](#); [Weikert et al., 2009](#)), increasing frequency of consumption ([Friborg et al., 2007](#); [Muwonge et al., 2008](#)), and duration of consumption ([Muwonge et al., 2008](#)). In one case-control study conducted in Taiwan, China among patients attending a hospital clinic ([Yen et al., 2008](#)) no association was found among non-smokers and a positive association among drinkers and smokers (Table 2.4 available at <http://monographs.iarc.fr/ENG/Monographs/>

[vol100E/100E-06-Table2.4.pdf](#)). [No information on the quantity of alcohol or tobacco consumption was available.] In a case-control study in Uruguay ([De Stefani et al., 2009](#)) a significant positive association with a predominantly alcohol-based dietary pattern and cancer of the oral cavity and pharynx was found (data not shown). [No specific assessment of alcohol intake was presented and the contribution of other foods to this dietary pattern was not known.]

Undifferentiated nasopharyngeal carcinoma (NPC), which is common in parts of Southern Asia, North Africa and the Arctic, is associated with Epstein-Barr virus and preserved foods (see the *Monograph* on Chinese-style Salted Fish in this volume). [Friborg et al. \(2007\)](#) confirmed earlier results suggesting limited or no association between alcohol and undifferentiated NPC ([Yu et al., 2002](#)). However, in a Western population where differentiated forms of NPC are more common, a significantly increased risk of NPC has been associated with heavy drinking (> 21 drinks per week) ([Vaughan et al., 1996](#)), indicating a difference in etiology between differentiated and undifferentiated types of NPC (Table 2.4 on-line).

[Thygesen et al. \(2009\)](#) reported a significantly higher rate of cancer of the oral cavity and pharynx among Danish alcohol abusers compared with national rates. [This cohort study provided no information on individual exposures or results adjusted for potential confounders.] See Table 2.5 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.5.pdf>.

(b) Intensity and duration

Previous studies consistently showed that consumption of alcoholic beverages is associated with an increased risk of cancer of the oral cavity and/or pharynx, although the nature of the dose-response relationship is not fully understood ([IARC, 2010](#)). In most studies an approximate threefold increased risk was found at relatively high levels of intake (i.e. > 60 g/day).

There is increasing evidence from recent cohort studies that risk may already be increased at more moderate intake, particularly in women ([Freedman et al., 2007a](#); [Allen et al., 2009](#); [Weikert et al., 2009](#)).

A pooled analysis of the International Head and Neck Cancer Epidemiology Consortium, which specifically examined the association of alcohol consumption and duration, found that among drinkers of 10 drinks per day or less, the association with total drink-years increased with increasing drinks/day, indicating that more drinks/day for a shorter duration was more deleterious than fewer drinks/day for a longer duration ([Lubin et al., 2009](#)).

(c) Effect of cessation

A meta-analysis of 13 case-control studies of cancer of the oral cavity and pharynx combined found that compared with current drinkers, risk did not decrease until 10 years or more after cessation of drinking (odds ratio (OR), 0.67; 95%CI: 0.63–0.73) ([Rehm et al., 2007](#)) (Table 2.6 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.6.pdf>). Consistent with many earlier studies, risks were found to be elevated among recent former drinkers, most likely due to ill health directly related to the cancer or its precursors.

(d) Types of alcoholic beverage

Some studies have assessed whether the association of consumption of alcoholic beverages on risk varies by beverage type, and have found broadly similar associations in wine, beer and spirit drinkers ([Freedman et al., 2007a](#); [Allen et al., 2009](#)).

(e) Population characteristics

The association of consumption of alcoholic beverages with risk of cancer of the oral cavity and pharynx is increased in both men and women ([Freedman et al., 2007a](#); [Weikert et al., 2009](#)).

Studies have been hampered with low numbers of women at the highest levels of exposure.

(f) *Histological subtype*

Very few studies have examined the association of consumption of alcoholic beverages by histological subtype for cancers of the oral cavity and pharynx. From a large-scale cohort study, [Weikert et al. \(2009\)](#) reported that both baseline and lifetime alcohol intake were associated with an increased risk of squamous cell carcinoma of the oral cavity and the pharynx, with an increased risk of 10% (95%CI: 8–13%) per 10 g per day increase in lifetime alcohol intake.

(g) *Association among non-smokers*

There is evidence from a pooled analysis of 15 case-control studies that increasing consumption of alcoholic beverages increases risk of cancer of the oral cavity and oropharynx/hypopharynx cancer among never smokers, with risk estimates of 1.23 (95%CI: 0.59–2.57) and 5.50 (95%CI: 2.26–13.36), for 5 or more drinks/day versus never drinkers, for the two cancer sites, respectively ([Hashibe et al., 2007](#); Table 2.6 on-line). One study in Taiwan, China found no association with alcohol consumption among non-smoking ever-drinkers for cancer of the oral cavity ([Yen et al., 2008](#)). [No information was provided on the quantity of alcohol consumed.]

(h) *Joint effect of alcoholic beverages and tobacco smoking*

It is well established that there is a joint effect of tobacco smoking and consumption of alcoholic beverages on the risk of cancer of the oral cavity and pharynx, with very high risks observed in individuals who are both heavy drinkers and heavy smokers, corresponding to a greater than a multiplicative interaction ([IARC, 2010](#)). The joint effect of alcohol consumption and tobacco smoking on the risk of cancers of the oral cavity

and pharynx is described in Section 2.20 of the *Monograph* on Tobacco Smoking in this volume.

2.2.2 *Cancer of the larynx*

It was concluded in the previous *IARC Monograph* ([IARC, 2010](#)) that consumption of alcoholic beverages is causally related to cancer of the larynx, and that the risk increases in a dose-dependent manner.

(a) *Overview of cohort and case-control studies*

Since [IARC \(2010\)](#), the association of consumption of alcoholic beverages and risk of cancer of the larynx has been assessed in three general-population cohort studies ([Freedman et al., 2007a](#); [Allen et al., 2009](#), [Weikert et al., 2009](#); Table 2.7 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.7.pdf>) and one case-control study ([Garavello et al., 2006](#); Table 2.8 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.8.pdf>), all of which found significant increases in risk associated with alcohol consumption. In one further case-control study in Uruguay ([De Stefani et al., 2009](#)) a significant positive association with a predominantly alcohol-based dietary pattern and cancer of the larynx was found (data not shown). [No specific assessment of alcohol intake was presented and the contribution of other foods to this dietary pattern was not known.]

[Thygesen et al. \(2009\)](#) reported a significantly higher rate of cancer of the larynx among Danish alcohol abusers compared with national rates (Table 2.5 on-line). This study provided no information on individual exposures or results adjusted for potential confounders

(b) *Intensity and duration*

Previous studies consistently showed that increasing alcohol consumption is associated with an increased risk of cancer of the larynx ([IARC, 2010](#)). [Bagnardi et al. \(2001\)](#) reported risk

estimates of 1.38 (95%CI: 1.32–1.45) for intake of 25 g alcohol per day, 1.94 (95%CI: 1.78–2.11) for 50 g per day, and 3.95 (95%CI: 3.43–4.57) for 100 g per day from a meta-analysis of 20 case–control studies, including over 3500 cases. An increased risk for cancer of the larynx was found for women drinking above one drink/day in a large cohort of United Kingdom women [equivalent to an increased risk of 1.44 (95%CI: 1.10–1.88) per 10 g alcohol per day] (Allen *et al.*, 2009). This is consistent with the 1.38 (95%CI: 1.10–1.73) estimate per 10 g per day reported among women in the European Prospective Investigation into Cancer and Nutrition (Weikert *et al.*, 2009). Compatible with this, Freedman *et al.* (2007a) reported a risk estimate of 2.15 (95%CI: 0.82–5.65) among women associated with 3 or more drinks/day from the NIH-AARP Diet and Health Study. Among men, the dose–response relationship is slightly weaker (Freedman *et al.*, 2007a; Weikert *et al.*, 2009), although it is difficult to determine whether these differences are due to chance because of the relatively low number of cases in women. In a large case–control study in Italy there was clear evidence of a dose–response relationship for men and women combined (Garavello *et al.*, 2006).

A pooled analysis of the International Head and Neck Cancer Epidemiology Consortium, which specifically examined the association of quantity and duration of alcohol consumption, found that among drinkers of 10 drinks per day or less, the association with total drink-years increased with increasing drinks/day, indicating that more drinks/day for a shorter duration was more deleterious than fewer drinks/day for a longer duration (Lubin *et al.*, 2009).

(c) *Effect of cessation*

Few studies have assessed whether the risk for cancer of the larynx declines since stopping drinking. Altieri *et al.* (2002) reported a risk estimate of 0.53 (95%CI: 0.15–1.94) for stopping drinking for 20 years or more ago compared with

current drinkers; the risk for never-drinkers was 0.56 (95%CI: 0.31–0.99).

(d) *Types of alcoholic beverage*

Evidence suggests that the most frequently consumed beverage in a population tends to be associated with the highest risk of cancer of the larynx. Data published recently largely supports this view (Garavello *et al.*, 2006). The NIH-AARP Diet and Health Study found a stronger association for spirits than for beer or wine consumption among men (Freedman *et al.*, 2007a). [The Working Group noted the small number of cases.]

(e) *Risk among non-smokers*

There is evidence from a pooled analysis of 11 case–control studies, based on 121 cases of laryngeal cancer, that increasing alcohol consumption increases the risk for cancer of the larynx among never smokers, with a risk estimate of 2.98 (95%CI: 1.72–5.17) for 5 or more drinks/day versus never drinkers (Hashibe *et al.*, 2007; Table 2.6 on-line).

(f) *Joint effect of alcoholic beverages and tobacco smoking*

Evidence suggests that there exists a joint effect of tobacco smoking and consumption of alcoholic beverages on the risk of cancer of the larynx, with very high risks observed in individuals who are both heavy drinkers and heavy smokers. More recent studies that have examined the joint effect of alcohol consumption and tobacco smoking on the risk of cancer of the larynx are described in Section 2.20 of the *Monograph on Tobacco Smoking* in this volume.

2.2.3 *Cancer of the oesophagus*

It was concluded in the previous *IARC Monograph* (IARC, 2010) that consumption of alcoholic beverages is causally associated with cancer of the oesophagus. The increased risk is

largely restricted to squamous cell carcinoma, with little or no association for adenocarcinoma of the oesophagus.

(a) *Overview of cohort and case–control studies*

Since [IARC\(2010\)](#), the association of consumption of alcoholic beverages and risk of cancer of the oesophagus has been assessed in six cohort studies ([Freedman et al., 2007b](#); [Ozasa et al., 2007](#); [Fan et al., 2008](#); [Allen et al., 2009](#); [Ishiguro et al., 2009](#); [Weikert et al., 2009](#); Table 2.9 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.9.pdf>) and four case–control studies ([Lee et al., 2005](#); [Vioque et al., 2008](#); [Benedetti et al., 2009](#); [Pandeya et al., 2009](#); Table 2.10 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.10.pdf>), all of which found significant increases in risk with alcohol consumption. A case–control study in Uruguay ([De Stefani et al., 2009](#)) found a significant positive association with a predominantly alcohol-based dietary pattern and cancer of the oesophagus (data not shown). [No specific assessment of alcohol intake was presented and the contribution of other foods to this dietary pattern was not known.]

[Thygesen et al. \(2009\)](#) reported a significantly higher rate of cancer of the oesophagus among Danish alcohol abusers compared with national rates (Table 2.5 on-line). [This study provided no information on individual exposures or results adjusted for potential confounders.]

(b) *Intensity and duration*

Data reviewed previously ([IARC, 2010](#)) consistently showed that increasing consumption of alcoholic beverages is associated with an increased risk of cancer of the oesophagus. Consistently, a 3–8 fold increased risk with high intakes of alcohol has been reported in more recent studies ([Lee et al., 2005](#); [Freedman et al., 2007b](#); [Ozasa et al., 2007](#); [Fan et al., 2008](#); [Vioque et al., 2008](#); [Ishiguro et al., 2009](#); [Pandeya et al., 2009](#)). Smaller increases in risk at lower amounts

of alcohol intake have been found by analysis of large cohorts in Europe, with a significant increased risk of approximately 20% per 10 g alcohol per day ([Allen et al., 2009](#); [Weikert et al., 2009](#)).

In several studies an increased risk has been found with duration of drinking ([Lee et al., 2005](#); [Ozasa et al., 2007](#); [Fan et al., 2008](#), [Vioque et al., 2008](#)), frequency of drinking ([Ozasa et al., 2007](#)), a lower age at starting drinking ([Ozasa et al., 2007](#); [Fan et al., 2008](#)), or cumulative intake ([Benedetti et al., 2009](#)). Risk is similar when alcohol consumption is based on measures of either baseline or lifetime alcohol consumption ([Fan et al., 2008](#); [Weikert et al., 2009](#)).

(c) *Effect of cessation*

In several studies the risk for cancer of the oesophagus was reduced with increasing time since cessation of drinking. In a meta-analysis of 5 case–control studies [Rehm et al. \(2007\)](#) reported that compared with current drinkers, risk was not reduced until 5 years or more after cessation of drinking (OR, 0.85; 95%CI: 0.78–0.92) and approached that of nondrinkers after 15 years or more since quitting drinking (Table 2.6 on-line). Similar results were obtained from a cohort study ([Ozasa et al., 2007](#)). Risks are elevated among more former drinkers, who most likely cease drinking due to ill health directly related to the cancer or its precursors ([Rehm et al., 2007](#); [Vioque et al., 2008](#); [Ozasa et al., 2007](#)).

(d) *Types of alcoholic beverage*

Most previous studies found no material difference in the association of consumption of alcoholic beverages on risk of cancer of the oesophagus according to specific beverage types, with the most commonly consumed beverage tending to be associated with the highest risk. This is supported by data from more recent studies ([Lee et al., 2005](#); [Freedman et al., 2007b](#); [Fan et al., 2008](#); [Vioque et al., 2008](#); [Allen et al., 2009](#); [Pandeya et al., 2009](#)).

(e) Population characteristics

All recent studies have found significant positive associations in both men ([Fan et al., 2008](#); [Benedetti et al., 2009](#); [Ishiguro et al., 2009](#)) and women ([Allen et al., 2009](#)), and in studies that have stratified by sex ([Pandeya et al., 2009](#)).

(f) Risk associated with facial flushing response

One cohort study in Japan examined the association of consumption of alcoholic beverages with cancer of the oesophagus according to whether the cohort members experienced a facial flushing response. Although the risk associated with a high alcohol intake among men with a flushing response was higher than among those with no flushing response, the differences were not significant. Details of the association of alcohol consumption according to genetic variants in alcohol-metabolizing genes related to the flushing response are presented in Section 2.19.

(g) Histological subtypes

In the previous *IARC Monograph* it was concluded that consumption of alcoholic beverages is causally related to squamous cell carcinoma of the oesophagus (OSCC), with no or little association with adenocarcinoma of the oesophagus ([IARC, 2010](#)). Data published since a strong association with OSCC or non-adenocarcinoma ([Lee et al., 2005](#); [Freedman et al., 2007b](#); [Fan et al., 2008](#); [Vioque et al., 2008](#); [Allen et al., 2009](#); [Benedetti et al., 2009](#); [Ishiguro et al., 2009](#); [Pandeya et al., 2009](#); [Weikert et al., 2009](#)), and no association with alcohol consumption and adenocarcinoma of the oesophagus ([Freedman et al., 2007b](#); [Allen et al., 2009](#); [Benedetti et al., 2009](#); [Pandeya et al., 2009](#)).

(h) Association among non-smokers

Data on the association of consumption of alcoholic beverages with risk of cancer of the oesophagus among non-smokers are limited. [Pandeya et al. \(2009\)](#) reported higher risks with

increasing alcohol consumption among current smokers compared to never smokers from a case-control study in Australia. [The low numbers of highly exposed cases among never smokers makes it difficult to draw any conclusions.]

(i) Joint effect of alcoholic beverages and tobacco smoking

Evidence suggests a joint effect of tobacco smoking and consumption of alcoholic beverages on the risk for cancer of the oesophagus, with very high risks observed in individuals who were both heavy drinkers and heavy smokers. Recent studies that have examined the joint effect of alcohol consumption and tobacco smoking on the risk of cancer of the oesophagus are described in Section 2.20 of the *Monograph* on Tobacco Smoking in this volume.

*2.2.4. Cancers of the upper aerodigestive tract combined**(a) Overview of cohort and case-control studies*

In the previous *IARC Monograph* ([IARC, 2010](#)) the association between consumption of alcoholic beverages and risk of cancer of the upper aerodigestive tract combined was not evaluated. Since then, three cohort studies ([Thygesen et al., 2007](#); [Allen et al., 2009](#); [Weikert et al., 2009](#); Table 2.11 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.11.pdf>) and one case-control study ([Zaridze et al., 2009](#); Table 2.12 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.12.pdf>) have examined the association of alcoholic beverage consumption and cancers of the upper aerodigestive tract (i.e. oral cavity, pharynx, larynx and oesophagus combined), and one reported on cancers of the oral cavity, pharynx and larynx combined ([Freedman et al., 2007a](#)). All studies reported significant increases in risk with alcoholic beverage consumption, observed in both men and women ([Freedman](#)

[et al., 2007a](#); [Thygesen et al., 2007](#); [Allen et al., 2009](#); [Weikert et al., 2009](#); [Zaridze et al., 2009](#)).

(b) *Intensity and duration*

In one cohort study an increased risk for cancer of the upper aerodigestive tract combined was observed only among those who had a relatively high alcohol intake (i.e. 42 drinks/week or more) ([Thygesen et al., 2007](#)). Other studies have reported increases in risk at more moderate levels of consumption, particularly among women ([Freedman et al., 2007a](#); [Allen et al., 2009](#); [Weikert et al., 2009](#)).

(c) *Types of alcoholic beverage*

The association of consumption of alcoholic beverages on risk of cancer of the upper aerodigestive tract combined does not vary by beverage type, as found in a meta-analysis of 15 case-control studies ([Purdue et al., 2009](#); Table 2.6 on-line) and cohort studies ([Allen et al., 2009](#); [Weikert et al., 2009](#)).

(d) *Association among non-smokers*

Few studies have had sufficient statistical power to assess reliably the association of consumption of alcoholic beverages by smoking status with cancers of the upper aerodigestive tract combined. Most previous studies (as outlined in [IARC, 2010](#)), as well as recent data from the European Prospective Investigation into Cancer and Nutrition have found similar increased risks with increasing alcohol intake among both non-smokers and smokers ([Weikert et al., 2009](#)). In a large cohort study among women in the United Kingdom with a low to moderate alcohol intake, alcohol consumption was not associated with an increased risk of cancers of the upper aerodigestive tract in never smokers or former smokers, but was strongly associated with an increased risk among current smokers ([Allen et al., 2009](#)).

2.3 Cancer of the colorectum

In the previous *IARC Monograph* ([IARC, 2010](#)) it was concluded that consumption of alcoholic beverages is causally related to cancer of the colorectum. This conclusion was largely based on a pooled analysis of eight cohort studies of alcohol intake and cancer of the colorectum conducted in Europe and North America, which found a relative risk (RR) of about 1.4 for cancer of the colorectum with regular consumption of high intakes of alcohol (≥ 45 g/d), compared to non-drinkers, in men and women combined, and which was not related to beverage type ([Cho et al., 2004](#)).

2.3.1 Cohort studies and meta-analyses of cohort studies

Since [IARC \(2010\)](#), 12 cohort studies have evaluated the association between consumption of alcoholic beverages and risk of cancer of the colorectum and/or cancer of the colon and rectum separately (Table 2.13 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.13.pdf>). Of the nine cohort studies that examined the association of consumption of alcoholic beverages and risk of cancer of the colorectum, seven confirmed a significant positive association ([Akhter et al., 2007](#); [Ferrari et al., 2007](#); [Ishihara et al., 2007](#); [Tsong et al., 2007](#); [Bongaerts et al., 2008](#); [Thygesen et al., 2008b](#); [Toriola et al., 2008](#)). In only two cohort studies was no overall association reported, although both of these likely included very few cases with a high alcohol intake ([Kabat et al., 2008](#); [Lim & Park, 2008](#)). In one further study ([Engeset et al., 2009](#)) no association with a predominantly alcohol-based dietary pattern and cancer of the colorectum was found. [No quantitative assessment of alcohol intake per se was provided and the contribution of other foods to this dietary pattern was not known.] Of the seven studies that evaluated cancer of the colon and rectum

separately ([Akhter et al., 2007](#); [Ferrari et al., 2007](#); [Ozasa, 2007](#); [Tsong et al., 2007](#); [Thygesen et al., 2008b](#); [Bongaerts et al., 2008](#); [Allen et al., 2009](#)), three reported a significant increased risk with alcohol intake for both sites ([Akhter et al., 2007](#); [Ferrari et al., 2007](#); [Tsong et al., 2007](#)). This is consistent with findings from one meta-analysis and one pooled analysis (Table 2.14 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.14.pdf>). In a meta-analysis of 21 cohort studies a significant increased risk for cancer of the colorectum, and for colon and rectal cancer separately, for heavy drinkers compared to light or non-drinkers was found ([Huxley et al., 2009](#)). There was also a significant positive association of consumption of alcoholic beverages for men and women with both cancer of the colon and of the rectum in a pooled analysis of five cohort studies in Japan ([Mizoue et al., 2008](#)). [Thygesen et al. \(2008b\)](#) reported an increased risk for colon cancer and not for rectal cancer; in two other studies a significant increased risk for rectal cancer and a weaker, non-significant positive association for colon cancer was found ([Ozasa, 2007](#); [Bongaerts et al., 2008](#)). [Such inconsistency may be due to the small numbers of heavy drinkers in each subsite.] In the largest study to date, with over 4000 cases of colon and over 2000 cases of rectal cancer, no association of alcohol intake was found with colon cancer and a small, but statistically significant, increased risk for rectal cancer ([Allen et al., 2009](#)). [The Working Group noted that the reason for the lack of association with colon cancer in this study of United Kingdom women is not clear, but may, in part, relate to the narrower range of alcohol intake (which was mostly low to moderate), resulting in limited power to detect an association at higher levels of alcohol intake]. Most of the studies in which the association of alcohol intake has been examined by more detailed subsite definitions within the colon are more consistent in showing a positive association with alcohol intake for cancer of

the distal colon, but a weak or null association for cancer of the proximal colon ([Akhter et al., 2007](#); [Ferrari et al., 2007](#); [Bongaerts et al., 2008](#); [Thygesen et al., 2008b](#)).

2.3.2 Cohort studies in special populations

Since [IARC \(2010\)](#), in one cohort study in the Netherlands a significantly higher rate of rectal cancer among male alcohol abusers compared with national rates, but no association with colon cancer was found (Table 2.15 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.15.pdf>). Among women, rates of both colon and rectal cancer were similar among alcohol abusers and the national population, although there were relatively low numbers for each cancer site ([Thygesen et al., 2009](#)). [This study provided no information on individual exposures or results adjusted for potential confounders.]

2.3.3 Case–control studies

Since [IARC \(2010\)](#), reports on the association of consumption of alcoholic beverages and cancer of the colorectum have come from 10 case–control studies. There was a significant positive association in five, three of which found an increased risk of cancer of the colorectum at relatively high levels of consumption ([Gao et al., 2008](#); [Lightfoot et al., 2008](#); [Benedetti et al., 2009](#)) and for two studies in the Far East an increased risk among drinkers was reported ([Sriamporn et al., 2007](#); [Wei et al., 2009](#)). [Information on quantity of intake was not available for these studies.] (Table 2.16 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.16.pdf>). No association for consumption of alcoholic beverages and cancer of the colorectum was reported for five case–control studies ([Wang et al., 2006a](#); [Murtaugh et al., 2007](#); [Pereira Serafim et al., 2008](#); [Ganesh et al., 2009](#); [Wu et al., 2009](#)). [These studies were conducted in populations with a low

intake of alcoholic beverages ([Wang et al., 2006a](#); [Murtaugh et al., 2007](#); [Ganesh et al., 2009](#)) and/or had a small sample size and limited exposure information ([Pereira Serafim et al., 2008](#); [Ganesh et al., 2009](#); [Wu et al., 2009](#)).

2.3.4 Dose–response relationship

One pooled analysis of eight cohort studies ([Cho et al., 2004](#)) and several independent studies found an increased risk for cancer of the colorectum for an alcohol intake of 20 g/day or more ([Gao et al., 2008](#)), 30 g/day or more ([Ferrari et al., 2007](#); [Bongaerts et al., 2008](#)) or 45 g/day or more ([Akhter et al., 2007](#)). A pooled analysis of five cohort studies conducted in Japan also found an increased risk for cancer of the colorectum above 23 g/day, evident for both cancer of the colon and of the rectum for both men and women ([Mizoue et al., 2008](#)). Other studies found an increased risk for cancer of the colorectum or rectum only with lower amounts of alcohol (i.e. of the order of 1 drink/d or 10 g/d) ([Tsong et al., 2007](#); [Thygesen et al., 2008b](#); [Allen et al., 2009](#)).

2.3.5 Types of alcoholic beverage

(a) Other metrics of exposure

Few studies have examined the association between cancer of the colorectum and other metrics of exposure (average alcohol intake, over a lifetime or specifically during early adulthood, age at starting, duration). The limited evidence suggests that there is no strong association with duration of drinking in years or age at started drinking ([Ferrari et al., 2007](#); [Ozasa, 2007](#); [Wu et al., 2009](#)). In most earlier studies and some recent studies the risk associated with a baseline measure of intake is similar to a measure of average lifetime intake ([Ferrari et al., 2007](#); [Thygesen et al., 2008b](#)), [Benedetti et al. \(2009\)](#) reported an increased risk with increasing cumulative intake. There is also very limited information on whether the frequency of drinking is an

important determinant of risk. In three studies no association with frequency of alcohol intake (drinks/day) was found ([Ozasa, 2007](#); [Lim & Park, 2008](#); [Benedetti et al., 2009](#)), while in others the frequency of intake was associated with an increased risk among those with a high intake of alcohol (> 15 g/d), but not among those with lower intake of alcohol ([Mizoue et al., 2008](#); [Thygesen et al., 2008b](#)).

The association of consumption of alcoholic beverages and cancer of the colorectum does not appear to differ by beverage type ([Ferrari et al., 2007](#); [Tsong et al., 2007](#); [Bongaerts et al., 2008](#); [Thygesen et al., 2008b](#)).

2.3.6 Population characteristics

The association of consumption of alcoholic beverages and cancer of the colorectum appears to be similar for men and women ([Ferrari et al., 2007](#); [Bongaerts et al., 2008](#)). There is a causal association between cigarette smoking and risk for cancer of the colorectum (see the *Monograph on Tobacco Smoking* in this volume). Most studies of consumption of alcoholic beverages have adjusted for smoking status. In studies that stratified the analysis by smoking status most found an increased risk among both never and current smokers, with the risk estimates slightly higher in current or ever smokers compared to never smokers ([Akhter et al., 2007](#); [Ferrari et al., 2007](#); [Tsong et al., 2007](#)).

[Ferrari et al. \(2007\)](#) did not find a statistically significant interaction term between alcohol drinking and smoking with regard to cancers of the colorectum. [Tsong et al. \(2007\)](#) reported that the interaction effect between alcohol and smoking was not statistically significant on risk of cancer of the colorectum overall and rectal cancer alone (both $P > 0.19$), while the interaction effect on colon cancer risk was of marginal statistical significance ($P = 0.051$).

Few studies have examined whether the association of alcohol with cancer of the colorectum

varies by folate status; the European Prospective Investigation into Cancer and Nutrition found some evidence that the risk for colorectal cancer associated with alcohol intake was stronger in individuals with a low folate intake, but the interaction term was of marginal statistical significance ([Ferrari et al., 2007](#)), and two other studies found no evidence that the association of alcohol intake with risk differed according to intake of folate, or intake of related nutrients such as vitamin B6, vitamin B12 or methionine ([Ishihara et al., 2007](#); [Kabat et al., 2008](#)).

2.4 Cancer of the liver and hepatobiliary tract

In the previous *IARC Monograph* ([IARC, 2010](#)) it was concluded that consumption of alcoholic beverages is causally related to risk of cancer of the liver. This conclusion was based on a considerable number of cohort and case-control studies.

Chronic infection with hepatitis viruses B and C are the major causes of cancer of the liver. The increased risk associated with consumption of alcoholic beverages has been found consistently among individuals infected with hepatitis viruses as well as among uninfected individuals. Quantification of the effect of consumption of alcoholic beverages on the risk of cancer of the liver cannot be determined reliably since cirrhosis and other liver disorders that often predate cancer of the liver tend to lead to a decrease in or the cessation of consumption of alcoholic beverages many years before the occurrence of cancer of the liver.

The previous *IARC Monograph* did not separately evaluate the effect of consumption of alcoholic beverages on the risk of cholangiocarcinoma.

2.4.1 Hepatocellular carcinoma

Three cohort studies ([Gwack et al., 2007](#); [Ohishi et al., 2008](#); [Allen et al., 2009](#); Table 2.17 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.17.pdf>) and three case-control studies ([Hassan et al., 2008](#); [Benedetti et al., 2009](#); [Zaridze et al., 2009](#); Table 2.18 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.18.pdf>) on the general population and one cohort study on alcoholics ([Thygesen et al., 2009](#); Table 2.19 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.19.pdf>) have been identified since [IARC \(2010\)](#). No new meta-analysis or studies on the joint effect of alcohol beverage and virus infection were found.

In the three cohort studies, [Gwack et al. \(2007\)](#) in Republic of Korea, [Ohishi et al. \(2008\)](#) in Japan, and [Allen et al. \(2009\)](#) in the United Kingdom, an association between consumption of alcoholic beverages and cancer of the liver was found. [Hassan et al. \(2008\)](#) reported from a study in USA an increased risk for cancer of the liver in women with increasing alcohol consumption. Among men, the risk for cancer of the liver was only increased among those with an ethanol intake of ≥ 60 ml per day. [Zaridze et al. \(2009\)](#) found an increased risk of cancer of the liver with consumption of alcoholic beverages (usually vodka) among both men and women in the Russian Federation as did [Benedetti et al. \(2009\)](#) from Canada. [Thygesen et al. \(2009\)](#) reported a higher risk of cancer of the liver among both alcoholic men and women compared to the general population. [There were only 8 cases among women.]

2.4.2 Cholangiocarcinoma

Ten studies on the association between consumption of alcoholic beverages and cholangiocarcinoma (CCA) in the general population were identified ([Parkin et al., 1991](#); [Shin et al.,](#)

1996, [Donato et al., 2001](#); [Kuper et al., 2001](#); [Yamamoto et al., 2004](#); [Honjo et al., 2005](#); [Shaib et al., 2007](#); [Hsing et al., 2008](#); [Lee et al., 2008a](#); [Zhou et al., 2008](#)), all of which were case-control studies (Table 2.20 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.20.pdf>). An increased risk for cholangiocarcinoma among heavy drinkers (≥ 80 g/day) was reported in two studies from the Republic of Korea ([Shin et al., 1996](#) for CCA; [Lee et al., 2008a](#) for intrahepatic CCA) and one study from the USA ([Shaib et al., 2007](#) for both intrahepatic and extrahepatic CCA), among current drinkers in a study from China ([Hsing et al., 2008](#) for extrahepatic CCA), and among regular drinkers in Thailand ([Honjo et al., 2005](#) for CCA). In another study in Thailand a non-significant increased risk among regular drinkers was found ([Parkin et al., 1991](#) for CCA). There was no association in three studies on intrahepatic CCA from Italy ([Donato et al., 2001](#)), Japan ([Yamamoto et al., 2004](#)), and China ([Zhou et al., 2008](#)) (Table 2.20 on-line). [Kuper et al. \(2001\)](#) did not find any association between consumption of alcoholic beverages and cholangiocarcinoma in a low-risk Caucasian population in Greece [data not shown due to only six cases].

Cholangiocarcinoma is a recognized complication of primary sclerosing cholangitis. A study among patients with primary sclerosing cholangitis (26 cases of CCA following primary sclerosing cholangitis, 87 controls with primary sclerosing cholangitis) reported alcohol drinking as one of the risk factor for developing CCA ([Chalasani et al., 2000](#)).

2.5 Cancer of the stomach

In the previous *IARC Monograph* ([IARC, 2010](#)), results on the risk for cancer of the stomach associated with the consumption of alcoholic beverages were considered inconsistent. Since then, four cohort studies ([Freedman et al., 2007](#); [Larsson et al., 2007](#); [Sung et al., 2007](#); [Allen](#)

[et al., 2009](#)) and three case-control studies ([Lucenteforte et al., 2008](#); [Benedetti et al., 2009](#); [Zaridze et al., 2009](#)) in the general population, and one cohort study in alcoholics ([Thygesen et al., 2009](#)) have been published.

2.5.1 Cohort studies in the general population

Among cohort studies, no general association between alcohol intake and cancer of the stomach was found in three studies ([Freedman et al., 2007](#); [Larsson et al., 2007](#); [Allen et al., 2009](#)), while [Sung et al. \(2007\)](#) reported a slight increase in risk (Table 2.21 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.21.pdf>).

2.5.2 Cohort studies in special populations (alcohol abusers)

[Thygesen et al. \(2009\)](#) reported a higher risk of cancer of the stomach in alcoholics than in the general population (Table 2.22 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.22.pdf>). The increase was statistically significant in men (68 cases) but not in women (7 cases). [This study provided no information on individual exposures or results adjusted for potential confounders.]

2.5.3 Case-control studies

None of the case-control studies ([Lucenteforte et al., 2008](#); [Benedetti et al., 2009](#); [Zaridze et al., 2009](#); Table 2.23 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.23.pdf>) found an overall association between alcohol intake and risk for cancer of the stomach. [Benedetti et al. \(2009\)](#) reported a statistically significant increase in the risk of cancer of the stomach among those who consumed 1–6 drinks per week, but not among those who drank 7 or more per week.

2.5.4 Types of alcoholic beverage

Analyses by different types of alcoholic beverages are presented in Table 2.24 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.24.pdf>). [Larsson et al. \(2007\)](#) found an increased risk for cancer of the stomach with intake of medium or strong beer, while no effects were found with light beer, wine or hard liquor. [Freedman et al. \(2007\)](#) reported an increased risk for cancer of gastric cardia among those with high intake of hard liquor while no such association was found in the case of non-cardia gastric adenocarcinoma. [Benedetti et al. \(2009\)](#) reported a statistically significant increase in risk for cancer of the stomach among those who consumed 1–6 drinks per week of any of beer, wine or hard liquor, but not with those who drank 7 or more per week.

2.5.5 Confounding

In the previous Monograph, significantly increased risks were reported in some studies, including those from Japan, China, Poland and the Russian Federation. In no study was it possible to stratify or adjust fully for lifetime infection with *Helicobacter pylori*. It was concluded that since most of the population in areas where an association between consumption of alcoholic beverages and stomach cancer emerged had probably been infected by the bacterium, potential confounding by *H. pylori* infection was not a major concern. Of concern, however, was the likelihood that dietary deficiencies exist in those populations and that the consumption of alcoholic beverages might be accompanied by other unfavourable lifestyle factors, such as low socioeconomic class and low intake of fresh fruit, vegetables and various micronutrients ([IARC, 2010](#)).

New studies did not provide any additional information of potential confounders.

2.6 Cancer of the pancreas

In the previous *IARC Monograph* ([IARC, 2010](#)), it was concluded that there was not strong evidence for an association between the consumption of alcoholic beverages and risk of cancer of the pancreas.

2.6.1 Meta- and pooled analyses

A pooled analysis of 14 cohort studies ([Genkinger et al., 2009](#)) and a meta-analysis of 21 case-control studies and 11 cohort studies (one of which was the pooled analysis) ([Tramacere et al., 2009](#)) reported a small, statistically significant, increased risk for cancer of the pancreas associated with high intakes of alcoholic beverages (Table 2.25 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.25.pdf>). In the pooled analysis, with over 2000 incident cases of cancer of the pancreas, a relative risk of 1.22 (95%CI: 1.03–1.45) for those drinking ≥ 30 g/day versus none was found, with no significant difference by beverage type ([Genkinger et al., 2009](#)). [Tramacere et al. \(2009\)](#) reported a relative risk of 1.22 (95%CI: 1.12–1.34) for those drinking ≥ 3 drinks/day [approx. 30 g/day] versus none or occasional drinkers.

2.6.2 Cohort studies in the general population

In addition to the cohort studies included in the pooled analysis by [Genkinger et al. \(2009\)](#), the association of alcoholic beverage consumption and risk for cancer of the pancreas has been independently examined in six cohort studies (Table 2.26 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.26.pdf>). A nested case-control study within the Veterans Health Administration Cohort [the control population consisted of all participants without cancer of the pancreas enrolled in the study] found a significant negative association between alcohol use and cancer of the pancreas.

[Only data on current alcohol use were collected by the clinical provider, and duration and intensity of alcohol use were not recorded. It is possible that patients might have stopped drinking due to ill health, thereby causing a spuriously high risk among the non-drinkers ([Khurana et al., 2007](#)).] In another study, high alcohol consumption, defined according to a scoring system that was based on a self-administered questionnaire designed to detect alcoholism and on serum levels of γ -glutamyl transferase [a biomarker of excessive drinking], was associated with an increased risk for cancer of the pancreas ([Johansen et al., 2009](#)). [Data on the amount of alcohol consumption were not available.] In the Million Women Study in the United Kingdom, with approximately 1300 incident cases, there was no association between alcohol intake and risk for cancer of the pancreas among this population of low to moderate drinkers (only 5% drank ≥ 15 drinks/week) ([Allen et al., 2009](#)). In the European Prospective Investigation of nutrition and Cancer there was also no association with alcohol intake ([Rohrmann et al., 2009](#)), although there was some suggestion of an increased risk among those with a high average lifetime intake of spirits (RR for ≥ 10 g/day versus 0.1–4.9 g/day: 1.40; 95%CI: 0.93–2.10). This finding is based on small numbers and should be interpreted with caution, in the NIH-AARP study (based on over 1000 incident cases) there was also a positive association between high alcohol intake and risk for cancer of the pancreas (RR for ≥ 3 versus $> 0 - < 1$ drinks/day: 1.45; 95%CI: 1.17–1.80), which was stronger among those with a high intake of spirits (RR for ≥ 3 drinks/day versus $> 0 - < 1$ drinks/day: 1.62, 95%CI: 1.24–2.10); there was no association for increasing intake of beer or wine, although few participants were heavy wine or beer drinkers ([Jiao et al., 2009](#)). In the Netherlands Cohort Study the increased risk was limited to heavy drinkers (RR for ≥ 30 g/day versus none: 1.57; 95%CI: 1.03–2.39), and was similar in a subgroup of individuals who

reported a stable alcohol intake for the previous five years (RR for ≥ 30 g/day versus none: 1.82, 95%CI: 1.05–3.15), but there was no association with a specific beverage type ([Heinen et al., 2009](#)). The increased risk was observed only during the first 7 years of follow-up and not with longer follow-ups.

2.6.3 Cohort studies in special populations

In one cohort study conducted in the Netherlands there was a significantly higher rate of cancer of the pancreas among male alcohol abusers compared with the national average. Among women, rates of cancer of the pancreas were similar among alcohol abusers and the national population ([Thygesen et al., 2009](#); Table 2.27 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.27.pdf>). [The Working Group noted the low number of cases. This study provided no information on individual exposures or results adjusted for potential confounders.]

2.6.4 Case-control studies

In the previous *IARC Monograph* ([IARC, 2010](#)) reports of 29 case-control studies with quantitative data on the association of alcoholic beverage intake and the risk for cancer of the pancreas were considered. Most of these found no association, although some suggested that heavy alcoholic beverage drinking (e.g. ≥ 15 drinks/week) may be associated with an increased risk, while others found significant reductions in risk with increasing alcoholic beverage intake. Since then, four further case-control studies have been published (Table 2.28 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.28.pdf>). In a case-control study in the USA, with over 800 cases, a significant positive association with heavy consumption of alcoholic beverages and risk for cancer of the pancreas was found (≥ 60 versus < 60 mL ethanol/day: RR, 1.6;

95%CI: 1.1–2.5) ([Hassan et al., 2007](#)). A positive association with high lifetime consumption of alcohol, and which was strongest for intake of spirits, was found in a small study in Canada (with 83 cases) ([Benedetti et al., 2009](#)). In another study in Canada, with over 400 cases, no association with alcohol intake was found ([Anderson et al., 2009](#)). [In this study the range of alcohol intake was narrow and the response rate among the cases was low (24% of all identified cases; 45% of contacted living cases), which may have led to some response bias.] In a study conducted in the Russian Federation with 366 pancreatic cancer deaths no significant association between a very high intake of vodka and death from cancer of the pancreas was found; however, the numbers were small (52 men and 4 women in the highest intake group) and exposure information was obtained from proxies of the decedents [which may have led to some misclassification of exposure] ([Zaridze et al., 2009](#)). [Other studies with a high proportion of proxy respondents may also be prone to recall bias ([Benedetti et al., 2009](#)). On the other hand, given the lethality of the disease, studies that only included self-respondents ([Hassan et al., 2007](#)) may be prone to selection bias if alcohol consumption is associated with tumour aggressiveness.]

2.6.5 Patient characteristics

Some studies have shown higher risks in men than in women ([Heinen et al., 2009](#); [Jiao et al., 2009](#); [Zaridze et al., 2009](#)) [there were too few women in the highest category of alcohol intake to draw meaningful comparisons.] Most studies, including the meta- and pooled analyses, have found no significant difference in risk estimates between men and women ([Genkinger et al., 2009](#); [Rohrmann et al., 2009](#); [Tramacere et al., 2009](#)). No evidence of a significant interaction between alcohol intake and pancreatic risk was found by either smoking status ([Anderson et al., 2009](#); [Genkinger et al., 2009](#); [Heinen et al., 2009](#);

[Jiao et al., 2009](#); [Johansen et al., 2009](#); [Rohrmann et al., 2009](#)), folate intake ([Genkinger et al., 2009](#); [Heinen et al., 2009](#); [Jiao et al., 2009](#)) or body mass index ([Johansen et al., 2009](#); [Rohrmann et al., 2009](#)), although [Genkinger et al. \(2009\)](#) found that the association of alcohol consumption with risk was stronger among normal-weight individuals compared with overweight and obese individuals.

2.6.6 Potential confounders

Since individuals who consume high amounts of alcohol are also often smokers, it is possible that the positive association observed with alcohol intake may, in part, be due to residual confounding by smoking. In the pooled analysis no association with increasing alcohol consumption among non-smokers was found but a small increased risk among past and current smokers ([Genkinger et al., 2009](#)). Although these differences were not statistically significant, it suggests that residual confounding by smoking cannot be ruled out. Evidence from other smaller studies is inconsistent, perhaps due to the low numbers of heavily exposed cases among non-smokers ([Anderson et al., 2009](#); [Heinen et al., 2009](#); [Johansen et al., 2009](#); [Jiao et al., 2009](#); [Rohrmann et al., 2009](#)). [The Working Group noted that among smokers, it is difficult to disentangle the effects of alcohol from that of smoking due to differences in the amount of cigarettes consumed.]

2.7 Cancer of the lung

A possible link between consumption of alcoholic beverages and risk for cancer of the lung has long been speculated; in the previous *IARC Monograph* ([IARC, 2010](#)) it was concluded that the available data were inadequate to determine a causal association between the consumption of alcoholic beverages and lung cancer.

Two case-control studies ([Kubik et al., 2004](#); [Benedetti et al., 2009](#)), eight cohort studies ([Takezaki et al., 2003](#); [Nakaya et al., 2005](#); [Chao et al., 2008](#); [Shimazu et al., 2008](#); [Allen et al., 2009](#); [Thun et al., 2009](#); [Thygesen et al., 2009](#); [Toriola et al., 2009](#)), two meta-analyses ([Chao, 2007](#); [Fan & Cai, 2009](#)) and one systematic review ([Wakai et al., 2007](#)) were not considered in the previous IARC Monograph ([IARC, 2010](#)). More detailed analyses with regard to cancer of the lung for one of the case-control studies ([Benedetti et al., 2009](#)) were available in an earlier publication ([Benedetti et al., 2006](#)); therefore, the earlier publication is considered for this evaluation. This section reviews all available data.

A high correlation has been identified between tobacco smoking and alcohol drinking in many populations. As such, careful adjustment for smoking is one of the most important requirements for a valid interpretation for the association between alcohol drinking and cancer of the lung.

2.7.1 Overview of studies

(a) Cohort studies in the general population

Among 29 cohort studies of the general population that provided tobacco smoking-adjusted risk estimates for total alcoholic beverage use, of which one was a pooled analysis of seven cohort studies ([Freudenheim et al., 2005](#)), a significant elevated risk for cancer of the lung associated with alcoholic beverage consumption was reported in 16 ([Klatsky et al., 1981](#); [Pollack et al., 1984](#); [Stemmermann et al., 1990](#); [Chow et al., 1992](#); [Potter et al., 1992](#); [Doll et al., 1994](#); [Murata et al., 1996](#); [Prescott et al., 1999](#); [Lu et al., 2000](#); [Korte et al., 2002](#) [which includes two separate studies: the Cancer Prevention Study (CPS) I and II]; [Balder et al., 2005](#); [Nakaya et al., 2005](#); [Nishino et al., 2006](#); [Chao et al., 2008](#); [Toriola et al., 2009](#)) (the new studies are summarized in Table 2.29 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.29.pdf>).

In some of these studies an increased risk at high levels of consumption was found ([Klatsky et al., 1981](#); [Pollack et al., 1984](#); [Potter et al., 1992](#); [Doll et al., 1994](#); [Murata et al., 1996](#); [Prescott et al., 1999](#); [Lu et al., 2000](#); [Korte et al., 2002](#) [CPS I and II]; [Balder et al., 2005](#); [Nakaya et al., 2005](#); [Chao et al., 2008](#)), while no association at the highest consumption category but with moderate consumption was found in other studies ([Stemmermann et al., 1990](#); [Chao et al., 2008](#), [only for drinking < 1 drink beer per week versus non-drinkers]), among former drinkers ([Nakaya et al., 2005](#); [Nishino et al., 2006](#)), or among binge drinkers ([Toriola et al., 2009](#)). No significant association was observed in the other cohort studies with results adjusted for smoking, including the pooled analysis of seven cohorts ([Kvåle et al., 1983](#); [Kono et al., 1986](#); [Bandera et al., 1997](#); [Yong et al., 1997](#); [Woodson et al., 1999](#); [Breslow et al., 2000](#); [Djoussé et al., 2002](#); [Takezaki et al., 2003](#); [Freudenheim et al., 2005](#); [Rohrmann et al., 2006](#); [Shimazu et al., 2008](#); [Allen et al., 2009](#); [Thun et al., 2009](#)). In some of these studies, levels of alcohol intake among the participants were moderate ([Kono et al., 1986](#); [Breslow et al., 2000](#); [Freudenheim et al., 2005](#); [Allen et al., 2009](#)).

(b) Cohort studies in special populations

The risk for cancer of the lung among alcoholics or patients with alcohol use disorders was examined in seven cohort studies ([Schmidt & Popham, 1981](#); [Adami et al., 1992](#); [Tønnesen et al., 1994](#); [Sigvardsson et al., 1996](#); [Sørensen et al., 1998](#); [Boffetta et al., 2001](#); [Thygesen et al., 2009](#)) are summarized in Table 2.30 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.30.pdf>. All reported elevated risk of cancer of the lung. However, due to the lack of control for tobacco smoking in all of the studies, the observed association may be largely explained by the confounding effect of tobacco smoking.

(c) Case-control studies

In all, 22 case-control studies reported tobacco smoking-adjusted odds ratios for total consumption of alcoholic beverages and the risk for cancer of the lung (the new studies are summarized in Table 2.31 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.31.pdf>). In seven population-based studies (Koo, 1988; Bandera *et al.*, 1992; Mayne *et al.*, 1994; Carpenter *et al.*, 1998; Hu *et al.*, 2002; Freudenheim *et al.*, 2003; Benedetti *et al.*, 2006) and 11 hospital-based studies (Williams & Horm, 1977; Herity *et al.*, 1982; Kabat & Wynder, 1984; Mettlin, 1989; Pierce *et al.*, 1989; Rachtan & Sokolowski, 1997; Zang & Wynder, 2001; De Stefani *et al.*, 2002; Pacella-Norman *et al.*, 2002; Ruano-Ravina *et al.*, 2004; Kubík *et al.*, 2004) no significant association between any level of alcoholic beverage consumption and the risk for cancer of the lung was found, while in four hospital-based studies (De Stefani *et al.*, 1993; Dosemeci *et al.*, 1997; Rachtan, 2002; Gajalakshmi *et al.*, 2003) an association was found.

(d) Meta- and pooled analyses

Korte *et al.* (2002) found an increased risk for lung cancer with an ethanol intake of at least 2000 g per month (≥ 5 drinks/day): the relative risk from cohort studies was 1.53 (95%CI: 1.04–2.25) and the odds ratio from case-control studies was 1.86 (95%CI: 1.39–2.49) [the estimated risks for intake of 2000 g/month or more were based on only one study for both cohort and case-control studies]; lower intakes were not associated with increased risk (Table 2.32 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.32.pdf>). [The exposure studied most extensively was the frequency of drinking. Other parameters of alcoholic beverage exposure, such as duration and age at initiation of drinking and the relevant exposure period were not considered.] In another meta-analysis

Fan & Cai (2009) provided estimates for total alcohol drinking, and did not find a significant association with risk of lung cancer. In a pooled analysis of 7 cohort studies, Freudenheim *et al.* (2005) found a slightly greater risk of cancer of the lung with the consumption of ≥ 30 g alcohol per day than with no alcohol consumption (RR, 1.21; 95%CI: 0.91–1.61 in men, RR, 1.16; 95%CI: 0.94–1.43 in women).

2.7.2 Types of alcoholic beverage

Findings from studies examining risk estimates for the consumption of different types of alcoholic beverages (i.e. beer, wine, and hard liquor) have been inconsistent (Pollack *et al.*, 1984; Mettlin, 1989; Bandera *et al.*, 1992; Chow *et al.*, 1992; De Stefani *et al.*, 1993; Carpenter *et al.*, 1998; Prescott *et al.*, 1999; Woodson *et al.*, 1999; De Stefani *et al.*, 2002; Hu *et al.*, 2002; Rachtan 2002; Kubík *et al.*, 2004; Ruano-Ravina *et al.*, 2004; Freudenheim *et al.*, 2005; Benedetti *et al.*, 2006) (the new studies are summarized in Table 2.31 on-line). Risk estimates for different types of alcoholic beverages were also reported in two meta-analyses (Chao, 2007; Fan & Cai, 2009) using results adjusted for smoking (Table 2.32 on-line). Both found a slightly increased risk associated with beer drinking; there was also a slight association between drinking of liquor (Chao, 2007) and spirits (Fan & Cai, 2009) and risk for cancer of the lung. However, when one of the meta-analyses included only the studies with more comprehensive adjustments for smoking (Chao, 2007), there was no significant association.

2.7.3 Smoking status

Several cohort studies have examined the effect of alcoholic beverage consumption among both never smokers and smokers, and the interaction between these two risk factors (Korte *et al.*, 2002; Freudenheim *et al.*, 2005; Nishino *et al.*, 2006; Rohrmann *et al.*, 2006; Chao *et al.*, 2008;

[Shimazu et al., 2008](#); [Thun et al., 2009](#); [Toriola et al., 2009](#); Table 2.33 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.33.pdf>, and Table 2.34 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.34.pdf>). [Korte et al. \(2002\)](#) found an increased risk for cancer of the lung associated with drinking ≥ 500 g of alcohol per month among both never smoker men and women in CPS I but not in CPS II. In a pooled study of seven cohorts, [Freudenheim et al. \(2005\)](#) found an elevated pooled relative risk for alcoholic beverage consumption among never-smoking men but not among never-smoking women. A dose–response was also observed among men with a sixfold increase in risk among never smokers who consumed ≥ 15 g/day (pooled multivariate RR, 6.38; 95%CI: 2.74–14.90; *P* for trend < 0.001).

In contrast, [Nishino et al. \(2006\)](#), [Rohrmann et al. \(2006\)](#), [Shimazu et al. \(2008\)](#), [Thun et al. \(2009\)](#), and [Toriola et al. \(2009\)](#) reported no association among never smokers. [These analyses may have the limitation that most of the cases of cancer of the lung were smokers.] In a detailed analysis examining the effect of consumption of alcoholic beverages by smoking behaviour, [Woodson et al. \(1999\)](#) found no differences in the relative risks across smoking categories (< 20 , 20 – 29 , ≥ 30 cigarettes/day) [results were on smokers only]. However, [Shimazu et al. \(2008\)](#) found an increased risk for cancer of the lung among current smokers who drank 300–449 g ethanol per week (hazard ratio (HR), 1.66; 95%CI: 1.04–2.65) as well as those who drank ≥ 450 g/wk (HR, 1.69; 95%CI: 1.05–2.72; *P* for trend = 0.02) compared to current smokers who drank occasionally. [Toriola et al. \(2009\)](#) also found a significant positive association among smokers that was independent of the number of cigarettes smoked or the duration of smoking. However, the analysis was limited to binge drinkers.

Three case–control studies based on populations of never smokers ([Kabat & Wynder, 1984](#);

[Koo, 1988](#); [Hu et al., 2002](#)) found no significant risks for consumption of alcoholic beverages [There is a lack of power to examine the risk associated with heavy drinking, as it is uncommon to find heavy drinkers among never smokers.] In contrast, [Rachtan \(2002\)](#) observed a significantly elevated risk associated with alcoholic beverage intake among women who never smoked and a strong positive dose–response. Other studies on total alcohol intake with results stratified by smoking status have found positive associations between alcohol drinking and risk for cancer of the lung among smokers and no association among non-smokers ([Dosemeci et al., 1997](#); [Zang & Wynder, 2001](#)) or found associations among heavy smokers and no association among non-smokers and low/moderate-smokers combined ([Herity et al., 1982](#); [Bandera et al., 1992](#); [Benedetti et al., 2006](#) [men only]).

There is also some evidence that consumption of alcoholic beverages results in an inverse association with risk of cancer of the lung. Two studies reported an inverse association between wine consumption and lung cancer, one case–control study among non-smokers ([Kubík et al., 2004](#)) [results not adjusted for consumption of other alcoholic beverages], and one cohort study ([Chao et al., 2008](#)) among smokers.

2.7.4 Histological subtypes

Two cohort studies ([Rohrmann et al., 2006](#); [Shimazu et al., 2008](#)), one pooled analysis ([Freudenheim et al., 2005](#)) and eight case–control studies ([Koo, 1988](#); [Dosemeci et al., 1997](#); [Carpenter et al., 1998](#); [Zang & Wynder, 2001](#); [De Stefani et al., 2002](#); [Djousse et al., 2002](#); [Rachtan, 2002](#); [Benedetti et al., 2006](#)) presented smoking-adjusted risk estimates for consumption of alcoholic beverages by histological type of cancer of the lung (the new studies are summarized in Table 2.35 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.35.pdf>). There appears to be no consistent pattern of

effect estimates by histological type. [Estimates for subtype of cancer of the lung were mostly based on small numbers of cases, which leads to difficulties in interpreting results due to wide confidence intervals and the possibility of chance findings.] Few studies have reported results by histological type among never smokers ([Koo, 1988](#)).

2.7.5 Population characteristics

Several studies conducted analyses stratified by sex using the same exposure categories ([Williams & Horm, 1977](#); [Bandera et al., 1997](#); [Prescott et al., 1999](#); [Korte et al., 2002](#); [Pacella-Norman et al., 2002](#); [Freudenheim et al., 2005](#); [Benedetti et al., 2006](#); [Rohrmann et al., 2006](#)). No significant findings that differed by sex have been reported.

2.8 Cancer of the breast

2.8.1 Cancer of the female breast

The previous *IARC Monograph* ([IARC, 2010](#)) concluded that occurrence of cancer of the female breast was causally associated with the consumption of alcoholic beverages. This conclusion was based on data from more than 100 epidemiological studies, together with a pooled analysis of 53 studies on more than 58000 women with breast cancer, which found a linear increase in risk for breast cancer with increasing levels of alcoholic beverage consumption (increase per 10 g/d of 7.1%, 95%CI: 5.5–8.7%) ([Hamajima et al., 2002](#)).

(a) Cohort studies in the general population

Since [IARC \(2010\)](#), thirteen cohort studies have examined the association of consumption of alcoholic beverages and risk of cancer of the breast (Table 2.36 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.36.pdf>), eight of which showed a significant positive association ([Ericson et al., 2007](#);

[Mørch et al., 2007](#); [Zhang et al., 2007a](#); [Thygesen et al., 2008a](#); [Allen et al., 2009](#); [Duffy et al., 2009](#); [Lew et al., 2009](#); [Li et al., 2009b](#)), and four no significant association ([Trentham-Dietz et al., 2007](#); [Visvanathan et al., 2007](#); [Kabat et al., 2008](#); [Gibson et al., 2009](#)), [In two of these latter studies the number of drinkers was small and there was no quantitative assessment of alcohol intake.] One further study found no association with a predominantly alcohol-based dietary pattern and risk of cancer of the breast ([Engeset et al., 2009](#)) [No specific assessment of alcohol intake was presented and the contribution of other foods to this dietary pattern was not known.] The Million Women Study in the United Kingdom, with over 28 000 incident cancers, is the largest single study to estimate reliably the risk for cancer of the breast at low to moderate levels of alcohol consumption. A linear increase in risk of cancer of the breast with increasing alcohol intake (increase per 10 g/day [equivalent to about one drink regularly consumed per day] of 12%, 95%CI: 9–14%) was found ([Allen et al., 2009](#)). This estimate is slightly higher than the 7.1% increase in risk reported in the pooled analysis by [Hamajima et al. \(2002\)](#). [[Allen et al. \(2009\)](#) were able to take measurement error into account by repeating the alcohol consumption measure approximately three years after recruitment].

(b) Cohort studies in special populations

Since [IARC \(2010\)](#), [Thygesen et al. \(2009\)](#) reported a significantly higher rate of cancer of the breast among female alcoholics compared with national rates from a cohort study among Danish alcohol abusers (Table 2.37 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.37.pdf>) [This study provided no information on individual exposures or adjusted for potential confounders.]

(c) Case-control studies

The association of consumption of alcoholic beverages and risk for incident cancer of the female breast has been examined in 11 case-control studies (Table 2.38 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.38.pdf>). A significant positive association has been reported from six studies ([Beji & Reis, 2007](#); [Kruk, 2007](#); [Berstad et al., 2008](#); [Kocić et al., 2008](#); [Knight et al., 2009](#); [Newcomb et al., 2009](#)) and a significant inverse association in one ([Zaridze et al., 2009](#)). [This latter study was conducted in the Russian Federation where alcohol consumption is very high relative to other populations and exposure information was obtained from proxies of the decedents (case and control status was based on death certification information). Reasons for the inverse association with very high intake are not clear and information on potential confounders was unavailable.] Null associations were found in four studies ([Terry et al., 2007](#); [Bessaoud & Daurès, 2008](#); [Dolle et al., 2009](#); [Brown et al., 2010](#)), although they either had a very low alcohol intake ([Bessaoud & Daurès, 2008](#); [Dolle et al., 2009](#); [Brown et al., 2010](#)) or did not adjust for potential confounding factors ([Terry et al., 2007](#)).

(d) Other metrics of exposure

Very few investigators have examined whether the frequency of drinking, age at started drinking or the cumulative lifetime intake influences risk; in one cohort study in Denmark some evidence was found that binge drinking at the weekend may additionally increase risk ([Mørch et al., 2007](#)). Another cohort study in Denmark found that risk was attenuated when using updated alcohol information (i.e. most recent intake measured after recruitment), with the suggestion that there may be a long latent period between consumption of alcoholic beverages and development of cancer of the breast ([Thygesen et al., 2008a](#)). In contrast, [Berstad et al. \(2008\)](#)

reported a positive association for recent intake (i.e. in the last five years), but no association with lifetime intake or intake at a young age from a case-control study in the USA.

(e) Types of alcoholic beverage

There is consistent evidence from both cohort and case-control studies that the risk for cancer of the female breast does not vary significantly by beverage type ([Zhang et al., 2007a](#); [Berstad et al., 2008](#); [Bessaoud & Daurès, 2008](#); [Allen et al., 2009](#); [Lew et al., 2009](#); [Li et al., 2009b](#); [Newcomb et al., 2009](#)). Among wine drinkers, the risk does not vary by intake of red wine, white wine or a mixture of both ([Allen et al., 2009](#); [Newcomb et al., 2009](#)).

(f) Other factors affecting risk

There is consistent evidence that the association does not vary by folate intake ([Zhang et al., 2007a](#); [Duffy et al., 2009](#); [Lew et al., 2009](#)) or by menopausal status ([Mørch et al., 2007](#); [Terry et al., 2007](#); [Visvanathan et al., 2007](#); [Zhang et al., 2007a](#); [Kabat et al., 2008](#)), although in two case-control studies there was a slightly stronger association of consumption of alcoholic beverages and risk for cancer of the breast in postmenopausal than in premenopausal women ([Kruk, 2007](#); [Newcomb et al., 2009](#)).

It remains unclear whether the association of consumption of alcoholic beverages with risk of cancer of the breast varies by use of hormone-replacement therapy. In the Copenhagen City Heart Study, and to a lesser extent, the Women's Health Study, a positive association between alcohol intake and risk for cancer of the breast among current users, and no association among non-users of hormone-replacement therapy was found ([Zhang et al., 2007a](#); [Nielsen & Grønbaek, 2008](#)), whereas others have found no such differences ([Bessaoud & Daurès, 2008](#); [Allen et al., 2009](#); [Lew et al., 2009](#)).

Most of the data for an association of consumption of alcoholic beverages on risk for

cancer of the breast comes from Caucasian populations; there is very limited data among Asian populations (Gibson *et al.*, 2009; Brown *et al.*, 2010), perhaps due to the generally low prevalence of alcohol consumption. Most studies that included different ethnic groups estimated risk after adjusting for ethnicity; in two studies that stratified by ethnic group there was no difference in the risk associated with consumption of alcoholic beverages (Berstad *et al.*, 2008; Li *et al.*, 2009b).

There is accumulating evidence that cigarette smoking may increase risk for cancer of the breast (see Monograph on Tobacco Smoking in this Volume), and because drinking and smoking are highly correlated, most studies that have evaluated the association of consumption of alcoholic beverages on risk for cancer of the breast have adjusted for smoking, to a greater or lesser extent. Hamajima *et al.* (2002) found that the association of consumption of alcoholic beverages with risk for cancer of the breast was similar in never, ever and current smokers. No subsequent studies have had sufficient statistical power to evaluate this in more detail, although the evidence to date suggests that the association of consumption of alcoholic beverages on risk of cancer of the breast is unlikely to be confounded by smoking. Another potentially important confounder is body size; in those studies that have examined potential effect modification by body mass index no significant differences have been found (Zhang *et al.*, 2007a; Berstad *et al.*, 2008; Lew *et al.*, 2009).

(g) *Contralateral cancer of the breast*

The association of consumption of alcoholic beverages with risk for contralateral cancer of the breast was not evaluated in IARC (2010). To date, four cohort (Table 2.39 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.39.pdf>) and one case-control study (Table 2.40 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.40.pdf>)

[pdf](#)) have examined whether consumption of alcoholic beverages increases the risk of a subsequent contralateral cancer of the breast. In one cohort study alcohol consumption at the time of the first diagnosis and during the period between the first and second diagnosis was positively associated with the risk of contralateral cancer of the breast (Li *et al.*, 2009a), although no association was found in other cohort studies (Bernstein *et al.*, 1992; Li *et al.*, 2003b; Trentham-Dietz *et al.*, 2007). In the case-control study women with a contralateral breast cancer were more likely to have drunk regularly and to have drunk for a prolonged period of time compared with women who only had one diagnosis of cancer of the breast, although regular drinking during the period between the first and second diagnosis was not significantly associated with risk (Knight *et al.*, 2009).

(h) *Tumour receptor status*

The association of consumption of alcoholic beverages and risk for cancer of the breast by estrogen (ER) and progesterone (PR) receptor status has been examined in six cohort studies (Table 2.41 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.41.pdf>). Similar associations for ER+ and ER- tumours were reported by Chlebowski *et al.* (2007), Visvanathan *et al.* (2007), Lew *et al.* (2009) and Setiawan *et al.* (2009). Lew *et al.* (2009) found a slightly stronger association with alcohol intake and ER+/PR+ tumours than for ER+/PR- or ER-/PR- tumours. Li *et al.* (2009b) and Zhang *et al.* (2007a) in contrast reported positive associations for ER+ and PR+ tumours (together with the subgroup of ER+/PR+) and no association with ER- or PR- tumours. Tumour receptor status has also been evaluated in five case-control studies (Table 2.42 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.42.pdf>). In the largest, with approximately 1000 cases with information on receptor status, an increased risk for all

ER+ tumours, and no significant association for ER- tumours, irrespective of PR status, was found; the relative risk per 10 g alcohol/day for ER+/PR+ tumours was 1.14 (95%CI:1.07–1.20), that for ER+/PR- tumours was 1.07 (95%CI: 0.95–1.21) (Deandrea *et al.*, 2008). The association was slightly stronger among pre/perimenopausal women and among women with a high folate intake, although the numbers in these subgroups were small (Deandrea *et al.*, 2008). In a meta-analysis of 16 case-control studies and 3 cohort studies (Table 2.43 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.43.pdf>) an increased risk per 10 g/day increase in alcohol intake for all ER+ tumours was found (12% increased risk), and for the subtypes of ER+/PR+ tumours (11%) and ER+/PR- tumours (15%), and a smaller positive association for all ER- (7%), but no association with ER-/PR- or ER-/PR+ tumours (Suzuki *et al.*, 2008).

There are limited data on the association of consumption of alcoholic beverages with tumours that are characterized as triple-negative or basal-like (defined as ER-/PR-/HER2-), largely because of the recency of available data on HER2 status (human epidermal growth factor receptor). From a case-control study among premenopausal women Dolle *et al.* (2009) reported no association between consumption of alcoholic beverages with triple-negative or non triple-negative tumours, and in another case-control study no significant association with triple-negative or luminal B tumours (ER+ and/or PR+/HER2+) was found, but a stronger positive association for luminal A tumours (ER+ and/or PR+/HER2-) and HER2+ overexpressing tumours (defined as ER-/PR-/HER2+) (Trivers *et al.*, 2009). [The small numbers in some of these subgroups limits interpretation]. No significant differences in drinking status between women with luminal A tumours (the most common tumour type) and women diagnosed with triple-negative or HER2+ overexpressing tumours were

reported by Kwan *et al.* (2009) and Millikan *et al.* (2008) from case-only analyses; one found that women with luminal B tumours were less likely to be drinkers (Kwan *et al.*, 2009), while there was no difference in the other study (Millikan *et al.*, 2008). [The null associations seen for the rarer subtypes of ER+/PR- and ER-/PR+ tumours may reflect limited power of the studies.]

(i) *Histological subtype*

To date, the NIH-AARP (Lew *et al.*, 2009) is the only cohort study to have examined the association of consumption of alcoholic beverages by histological subtype among postmenopausal women; similar positive associations were reported for ductal, lobular and ductal-lobular subtypes (Table 2.44 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.44.pdf>). This is consistent with findings from one case-control study (Nasca *et al.*, 1994; Table 2.45 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.45.pdf>), while a slightly stronger positive association for alcohol intake with the risk for lobular tumours compared with ductal tumours, particularly among postmenopausal women, was found in two others (Li *et al.*, 2003a, 2006). [The low numbers of cases in some subgroups resulted in limited power to detect a significant difference, and these may be chance findings. In addition, it should be noted that the histological data from all of these studies was derived from hospital records and were not subject to central pathology review, leading to potential misclassification due to observer variability.]

2.8.2 *Cancer of the male breast*

It was concluded in the previous IARC Monograph (IARC, 2010) that the evidence for an association of consumption of alcoholic beverages and risk of cancer of the male breast was inconsistent.

(a) Cohort studies

Since [IARC \(2010\)](#), the association between consumption of alcoholic beverages and the risk for cancer of the male breast has been assessed in two cohort studies (Table 2.46 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.46.pdf>). In the NIH-AARP Study no evidence was found that alcohol intake was associated with the risk for cancer of the male breast ([Brinton et al., 2008](#)). In a large cohort of US Army Veterans no association with alcoholism as recorded from hospital records and risk for cancer of the male breast was found ([Brinton et al., 2009](#)).

(b) Studies in special populations

[Thygesen et al. \(2009\)](#) reported similar rates of cancer of the breast among male Danish alcoholics compared with national rates (Table 2.47 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.47.pdf>) [This was based on a very small number of cases and provided no information on individual exposures.]

2.9 Cancer of the uterine cervix

It was concluded in [IARC \(2010\)](#) that the evidence for an association between consumption of alcoholic beverages and risk for cancer of the uterine cervix was sparse. Although some studies of special populations showed positive associations, bias and confounding could not be excluded.

2.9.1 Cohort studies

The association between consumption of alcoholic beverages and risk for cancer of the uterine cervix has been examined in 8 cohort studies, seven of which were carried out in women who were treated for alcohol abuse or alcoholism ([Prior, 1988](#); [Adami et al., 1992](#);

[Tønnesen et al., 1994](#); [Sigvardsson et al., 1996](#); [Weiderpass et al., 2001](#); [Thygesen et al., 2009](#)) or worked as waitresses ([Kjaerheim & Andersen, 1994](#)), and one in the general population ([Allen et al., 2009](#)) (the new studies are summarized in Table 2.48 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.48.pdf>).

The majority of studies were conducted in Scandinavia ([Adami et al., 1992](#); [Kjaerheim & Andersen, 1994](#); [Tønnesen et al., 1994](#); [Sigvardsson et al., 1996](#); [Weiderpass et al., 2001](#); [Thygesen et al., 2009](#)), where the use of the unique identification numbers makes it possible to work on large, registry based data. Two cohort studies were conducted in the United Kingdom ([Prior, 1988](#); [Allen et al., 2009](#)). In all seven studies conducted in special populations elevated risk estimates for invasive cancer of the uterine cervix among alcoholic women were found compared to the general population. [None of the studies adjusted for known risk factors for cancer of the uterine cervix, namely human papilloma virus (HPV) infection, number of sexual partners and tobacco smoking, or attendance at cervical cancer screening programmes. It is possible that women with alcohol abuse have other behavioural patterns that may affect risk for cancer of the uterine cervix, such as non-compliance to screening, tobacco smoking and having a higher prevalence of HPV than the general population in their respective countries.]

In the Million Women Study ([Allen et al., 2009](#)) non-drinking women had an elevated risk for cancer of the uterine cervix compared to drinkers. Among drinkers, there was no association between the amount of alcohol consumed and risk for cancer of the uterine cervix. The analyses were adjusted for socioeconomic status, smoking, body mass index, physical activity, oral contraceptives and hormone replacement therapy use, but not for particular risk factors of cancer of the uterine cervix, including HPV infection and factors related to a sexual behaviour such as the

number of lifetime sexual partners or age at first intercourse.

2.9.2 Case-control studies

The association between consumption of alcoholic beverages and cancer of the uterine cervix was evaluated in 12 case-control studies, seven of which were hospital-based (two from Italy, two from Thailand, one from Uganda, one from United Kingdom, one from the USA), three were register or cohort based (from the USA and Zimbabwe), and two were based on both hospital and population controls (one from Lesotho and one large multicentric study from Latin America). No or no significant increased risk for cancer of the uterine cervix among alcoholic drinkers was found in eight studies ([Williams & Horm, 1977](#); [Harris et al., 1980](#); [Marshall et al., 1983](#); [Cusimano et al., 1989](#); [Licciardone et al., 1989](#); [Thomas et al., 2001a, b](#); [Chiaffarino et al., 2002](#)). In the three studies from Africa ([Martin & Hill, 1984](#); [Parkin et al., 1994](#); [Newton et al., 2007](#)), women who drank alcohol had a significant or borderline significant elevated risk for cancer of the uterine cervix. [Adjustment for confounding in these studies was incomplete.] In the study from Latin America, in which adjustment for possible confounders was adequate, there was an elevated risk for cancer of the uterine cervix among occasional drinkers (confidence intervals not given) but no association with heavy drinking ([Herrero et al., 1989](#)).

2.9.3 Evidence of a dose-response

The cohort studies on alcoholics did not provide convincing evidence of a dose-response between risk for cancer of the uterine cervix and duration of exposure, which was roughly estimated as years since cohort enrolment (first hospitalization/clinical treatment for alcoholism).

A case-control study from Latin America ([Herrero et al., 1989](#)), which adjusted for

important risk factors such as tobacco smoking and number of sexual partners, showed an inverse dose-response association. In four other case-control studies in which there was an indication of a higher risk for cancer of the uterine cervix with higher alcohol consumption, the observed association was weak in two ([Harris et al., 1980](#); [Marshall et al., 1983](#)) and significant in two other studies ([Martin & Hill, 1984](#); [Parkin et al., 1994](#)), but adjustment for possible confounders was incomplete. In one study, a positive trend was observed among consumers in the category “wine and other alcoholic beverages” ([Chiaffarino et al., 2002](#)).

2.9.4 Types of alcoholic beverage

The effect of specific types of alcoholic beverages (beer, wine and spirits) on risk for cancer of the uterine cervix was not investigated in the cohort studies.

In almost all case-control studies that evaluated specific types of alcoholic beverage ([Marshall et al., 1983](#); [Martin & Hill, 1984](#); [Chiaffarino et al., 2002](#)) no consistent differences in risk for cancer of the uterine cervix between drinkers and non-drinkers of a certain alcohol type were found. [Williams & Horm \(1977\)](#) found a non-significant higher risk for cancer of the uterine cervix among wine drinkers, while [Marshall et al. \(1983\)](#) found beer drinkers were at higher risk.

2.10 Cancer of the endometrium

In the previous *IARC Monograph* ([IARC, 2010](#)) it was concluded that the evidence for an association between consumption of alcoholic beverages and risk for cancer of the endometrium was inconsistent.

2.10.1 Cohort studies in the general population

The association between consumption of alcoholic beverages and cancer of the endometrium in the general population has been evaluated in eight cohort studies ([Gapstur et al., 1993](#); [Terry et al., 1999](#); [Folsom et al., 2003](#); [Loerbroks et al., 2007](#); [Kabat et al., 2008](#); [Setiawan et al., 2008](#); [Allen et al., 2009](#); [Friberg & Wolk, 2009](#)) (the new studies or updates are summarized in Table 2.49 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.49.pdf>). These studies were conducted in North America ([Gapstur et al., 1993](#); [Folsom et al., 2003](#); [Kabat et al., 2008](#); [Setiawan et al., 2008](#)) and in Europe, one in the Netherlands ([Loerbroks et al., 2007](#)), one in the United Kingdom ([Allen et al., 2009](#)) and two in Sweden ([Terry et al., 1999](#); [Friberg & Wolk, 2009](#)). Risk estimates adjusted for multiple possible confounders (body size and reproductive factors) were presented in seven reports ([Gapstur et al., 1993](#); [Terry et al., 1999](#); [Loerbroks et al., 2007](#); [Kabat et al., 2008](#); [Setiawan et al., 2008](#); [Allen et al., 2009](#); [Friberg & Wolk, 2009](#)) while only five of these ([Jain et al., 2000a](#) [an earlier report from the same study as [Kabat et al. \(2008\)](#) in which results were not adjusted for smoking]; [Loerbroks et al., 2007](#); [Setiawan et al., 2008](#); [Allen et al., 2009](#); [Friberg & Wolk, 2009](#)) adjusted the analysis of consumption of alcoholic beverages for smoking. Smoking showed non-significant negative association in almost all studies except for [Friberg & Wolk \(2009\)](#), where the risk estimates for cancer of the endometrium were decreased among never smokers, especially in women drinking more than 10 g of alcohol daily.

There was no clear evidence of association between consumption of alcoholic beverages and the risk for cancer of the endometrium in any of these studies. In four ([Terry et al., 1999](#); [Loerbroks et al., 2007](#); [Kabat et al., 2008](#); [Setiawan et al., 2008](#)) some elevated risk for cancer of

the endometrium among drinking women was found. Only [Setiawan et al. \(2008\)](#) reported a statistically significant association, which was among women who consumed more than 2 drinks per day. In one study ([Folsom et al., 2003](#)), an inverse association was found. No association was found in the other studies ([Gapstur et al., 1993](#); [Allen et al., 2009](#); [Friberg & Wolk, 2009](#)).

2.10.2 Cohort studies in special populations

Three earlier cohort studies examined the association between alcoholic beverage intake and the risk for cancer of the endometrium in special populations, namely women hospitalized or being treated for alcohol dependence ([Tønnesen et al., 1994](#); [Sigvardsson et al., 1996](#); [Weiderpass et al., 2001](#), which was an update of [Adami et al., 1992](#)). [Thygesen et al. \(2009\)](#) conducted the most recent study (Table 2.50 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.50.pdf>).

[Weiderpass et al. \(2001\)](#) found an inverse association between alcoholic beverage consumption and cancer of the endometrium. [The analytical models did not include important covariates that may have confounded the association, such as cigarette smoking and body size.] In the other studies, there was no evidence of an association.

2.10.3 Case-control studies

Case-control studies that have investigated the relationship between alcoholic beverage consumption and the risk for cancer of the endometrium were carried out in North America, Japan and western Europe. Eight of these were hospital-based ([La Vecchia et al., 1986](#); [Cusimano et al., 1989](#); [Austin et al., 1993](#); [Levi et al., 1993](#); [Parazzini et al., 1995a](#); [Kalandidi et al., 1996](#); [Petridou et al., 2002](#); [Hosono et al., 2008](#)), two were based on cases and controls from a cancer survey or registry database ([Williams & Horm, 1977](#); [Kato et al., 1989](#)) and eight were

population-based ([Webster et al., 1989](#); [Shu et al., 1991](#); [Swanson et al., 1993](#); [Goodman et al., 1997](#); [Newcomb et al., 1997](#); [Jain et al., 2000b](#); [McCann et al., 2000](#); [Weiderpass & Baron, 2001](#)). The most recent study ([Hosono et al., 2008](#)) is summarized in Table 2.51 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.51.pdf>)

Eleven studies ([Cusimano et al., 1989](#); [Kato et al., 1989](#); [Webster et al., 1989](#); [Austin et al., 1993](#); [Swanson et al., 1993](#); [Parazzini et al., 1995a](#); [Kalandidi et al., 1996](#); [Newcomb et al., 1997](#); [Weiderpass & Baron, 2001](#); [Petridou et al., 2002](#); [Hosono et al., 2008](#)) were designed to examine the association between consumption of alcoholic beverages, other lifestyle factors such as cigarette smoking, use of hormone replacement therapy and other risk factors in the etiology of cancer of the endometrium. Six studies ([LaVecchia et al., 1986](#); [Shu et al., 1991](#); [Levi et al., 1993](#); [Goodman et al., 1997](#); [Jain et al., 2000b](#); [McCann et al., 2000](#)) were designed to evaluate nutritional factors. Potentially confounding factors were considered in all the studies except for one ([Cusimano et al., 1989](#)), although adjustment may have been incomplete in three studies ([Williams & Horm, 1977](#), [age, race and smoking]; [Shu et al., 1991](#), [pregnancies and weight]; [Levi et al., 1993](#), [only adjusted for age and centre]).

The results of case-control studies were not consistent. In 10 studies little or no association between consumption of alcoholic beverages and the risk for cancer of the endometrium was found ([Kato et al., 1989](#); [Webster et al., 1989](#); [Austin et al., 1993](#); [Swanson et al., 1993](#); [Kalandidi et al., 1996](#); [Goodman et al., 1997](#); [Newcomb et al., 1997](#); [McCann et al., 2000](#); [Weiderpass & Baron, 2001](#); [Petridou et al., 2002](#)). An inverse association was found in three ([Williams & Horm, 1977](#); [Jain et al., 2000b](#); [Hosono et al., 2008](#)), which was significant in two ([Jain et al., 2000b](#); [Hosono et al., 2008](#)) among moderate drinking women. An increased risk for cancer of the endometrium with high consumption of alcoholic beverages

was found by [LaVecchia et al. \(1986\)](#), [Cusimano et al. \(1989\)](#), [Shu et al. \(1991\)](#), [Levi et al. \(1993\)](#) and [Parazzini et al. \(1995a\)](#); in two the association was non-significant ([Cusimano et al., 1989](#); [Shu et al., 1991](#)), in one it was significant ([Parazzini et al., 1995a](#)) and one ([Levi et al., 1993](#)) found a positive association relative to wine and liquor, but not to beer.

2.10.4 Evidence of a dose-response

There was no evidence of a trend of increasing risk for cancer of the endometrium with increasing consumption of alcoholic beverages in the cohort studies, nor a suggestion of a dose-response among long-term drinkers only ([Friberg & Wolk, 2009](#)).

In most case-control studies there was no dose-response relationship between consumption of alcoholic beverages and the risk for cancer of the endometrium. A negative dose-response association with significant trend was observed by [Jain et al. \(2000b\)](#) and [Hosono et al. \(2008\)](#), while one study showed a clear positive dose-response trend ([Parazzini et al., 1995a](#)). In another study, there was an indication of a negative dose-response in the association but no formal test for trend was presented ([Webster et al., 1989](#)).

2.10.5 Types of alcoholic beverage

The effect of specific types of alcoholic beverages (beer, wine, spirits) on the risk for cancer of the endometrium was investigated in three cohort studies, with no clear evidence of heterogeneity between different types of beverages ([Gapstur et al., 1993](#); [Loerbroks et al., 2007](#); [Setiawan et al., 2008](#)).

Consumption of different alcoholic beverages in relation to risk for cancer of the endometrium was evaluated in seven case-control studies ([Williams & Horm, 1977](#); [Austin et al., 1993](#); [Levi et al., 1993](#); [Swanson et al., 1993](#); [Parazzini](#)

[et al., 1995a](#); [Goodman et al., 1997](#); [Weiderpass & Baron, 2001](#)). [Levi et al. \(1993\)](#) and [Parazzini et al. \(1995a\)](#) found increased risk for cancer of the endometrium with increasing consumption of wine and hard liquor, but not beer. Overall, there were no consistent patterns of association between any specific type of alcoholic beverage and risk for cancer of the endometrium.

2.10.6 Interactions

Only [Setiawan et al. \(2008\)](#) reported detailed results of interaction between other risk factors and consumption of alcoholic beverages for cancer of the endometrium. There was no clear effect modification by body mass index, postmenopausal hormone use, parity, oral contraceptive use or smoking status, though the power to detect such interactions was limited. The Million Women Study Collaborators (2005) investigated alcohol only as an interacting factor with hormone replacement therapy and found no evidence for an effect modification. Results from stratified analyses did not show any effect modification by age, smoking, body mass index, folic acid intake, or postmenopausal hormone use ([Friberg & Wolk, 2009](#)).

2.11 Cancer of the ovary

In the previous *IARC Monograph* ([IARC, 2010](#)), it was concluded that the evidence for an association between consumption of alcoholic beverages and risk for cancer of the ovary in both cohort and case-control studies was sparse and inconsistent. Since [IARC \(2010\)](#), one cohort study in alcoholics ([Thygesen et al., 2009](#)) and one case-control study ([Kolahdooz et al., 2009](#)) have evaluated the association between consumption of alcoholic beverages and risk of cancer of the ovary.

2.11.1 Cohort studies

A total of five cohort studies have examined the association between consumption of alcoholic beverages and the risk for cancer of the ovary in special populations, women hospitalized or being treated for alcohol dependence, four early ([Adami et al., 1992](#); [Tønnesen et al., 1994](#), [Sigvardsson et al., 1996](#); [Lagiou et al., 2001](#)) and one more recent ([Thygesen et al., 2009](#); Table 2.52 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.52.pdf>); the association in the general population has been examined in seven cohort studies ([Kushi et al., 1999](#); [Kelemen et al., 2004](#); [Schouten et al., 2004](#); [Chang et al., 2007](#); [Kabat et al., 2008](#); [Tworoger et al., 2008](#); [Allen et al., 2009](#)). The studies were conducted in North America (USA and Canada) and Europe (the Netherlands, the United Kingdom and Scandinavia). The reports on studies in special populations presented results adjusted for age and calendar period only, whereas in the population based cohort studies results were adjusted for a large variety of factors.

There was no evidence of an overall association between consumption of alcoholic beverages and the risk for cancer of the ovary in these studies.

2.11.2 Case-control studies

Twenty-four case-control studies investigated the relationship between alcoholic beverage consumption and the risk for cancer of the ovary in North America, Japan, Australia, India, western Europe and Scandinavia, including one recent ([Kolahdooz et al., 2009](#); Table 2.53 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.53.pdf>). Eleven were hospital-based ([West, 1966](#); [Williams & Horm, 1977](#); [Byers et al., 1983](#); [Tzonou et al., 1984](#); [Mori et al., 1988](#); [Hartge et al., 1989](#); [LaVecchia et al., 1992](#); [Nandakumar et al., 1995](#); [Tavani et al., 2001a](#); [Yen et al., 2003](#); [Pelucchi et al., 2005](#)),

one was based on cases and controls who were included in a cancer registry database ([Kato et al., 1989](#)), 11 were population-based ([Gwinn et al., 1986](#); [Polychronopoulou et al., 1993](#); [Godard et al., 1998](#); [Kuper et al., 2000](#); [Goodman & Tung, 2003](#); [McCann et al., 2003](#); [Modugno et al., 2003](#); [Riman et al., 2004](#); [Webb et al., 2004](#); [Peterson et al., 2006](#); [Kolahdooz et al., 2009](#)) and one used controls chosen both among general population and hospital patients ([Whittemore et al., 1988](#)). The recent study ([Kolahdooz et al., 2009](#)) examined dietary patterns, including a predominantly snack and alcohol-based dietary pattern, and cancer of the ovary. [No specific assessment of alcohol intake was presented.] Confounding factors were considered in all studies, although adjustment was more extensive in more newly published studies than in studies published during the 1980s.

Overall, the results of case–control studies do not suggest any association between consumption of alcoholic beverages and risk for cancer of the ovary, although a few studies indicated either positive or negative associations.

2.11.3 Types of alcoholic beverage

In four population-based cohort studies the association with different types of alcoholic beverages was investigated ([Kelemen et al., 2004](#); [Schouten et al., 2004](#); [Chang et al., 2007](#); [Tworoger et al., 2008](#)). Intake of wine during the year before baseline was associated with an increased risk for cancer of the ovary in one study ([Chang et al., 2007](#)), but was not confirmed in the others ([Kelemen et al., 2004](#); [Schouten et al., 2004](#); [Tworoger et al., 2008](#)).

Seven case–control studies evaluated different alcoholic beverages in relation to risk for cancer of the ovary ([Gwinn et al., 1986](#); [LaVecchia et al., 1992](#); [Tavani et al., 2001a](#); [Goodman & Tung, 2003](#); [Modugno et al., 2003](#); [Webb et al., 2004](#); [Peterson et al., 2006](#)). Overall, there were no consistent patterns of association between any

specific type of alcoholic beverage (beer, wine and spirits) and risk for cancer of the ovary.

2.11.4 Interactions

[Kelemen et al. \(2004\)](#), [Schouten et al. \(2004\)](#) and [Chang et al. \(2007\)](#) evaluated their data for possible interaction between alcoholic beverage intake and other variables. [Kelemen et al. \(2004\)](#) found a statistically significant interaction between folate intake and alcohol consumption with regard to risk for cancer of the ovary. A similar association was observed by [Chang et al. \(2007\)](#) for women drinking more than one glass of wine daily. No other consistent interactions were reported. Among the case–control studies, there was no consistent evidence of interaction between alcoholic beverage consumption and different variables known or suspected to be associated with risk of cancer of the ovary, such as reproductive history, education, body size or diet.

2.12 Cancer of the prostate

In the previous *IARC Monograph* ([IARC, 2010](#)) it was concluded that the evidence for the association between consumption of alcoholic beverages and risk of cancer of the prostate is inconsistent. Increased risk for cancer of the prostate at elevated levels of consumption of alcoholic beverages was suggested from a few cohort studies, but there was no consistent dose–response relationship and in many cohort studies there was no association. The majority of case–control studies also showed no association between consumption of alcoholic beverages and cancer of the prostate.

2.12.1 Cohort studies in the general population

For studies of cancer of the prostate that were conducted more recently, there should be concern if no attempt is made to distinguish between cases that are detected by screening, with a possibility that many might not have presented clinically during the lifetime of the individual in the absence of screening, and those that present clinically and are more likely to be progressive. Among the 23 cohort studies six studies ([Platz et al., 2004](#); [Baglietto et al., 2006](#); [Sutcliffe et al., 2007](#); [Rohrmann et al., 2008](#); [Gong et al., 2009](#); [Chao et al., 2010](#); Table 2.54 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.54.pdf>) have considered the stage or grade of the disease. None found any association between alcoholic beverage consumption and risk of advanced cases of cancer of the prostate. However in one study ([Gong et al., 2009](#)) a strong association of increased risk of high-grade cancer of the prostate with heavy alcohol consumption in the whole study population was found (RR 2.01; 95%CI: 1.33–3.05), as well as among heavy beer drinkers (RR, 2.89; 95%CI: 1.76–3.76) compared to non-drinkers. In a few of the other cohort studies that did not make a distinction of cancer stage or grade there was an increased risk for cancer of the prostate at elevated levels of alcoholic beverage consumption ([Hirayama, 1992](#); [Schuurman et al., 1999](#); [Putnam et al., 2000](#); [Sesso et al., 2001](#)), but there was no consistent dose–response relationship. Many other cohort studies showed no association. The risk associated with different types of alcoholic beverages was inconsistent, with increased risks for both beer ([Gong et al., 2009](#)) and white wine consumption ([Velicer et al., 2006](#)), as well as null associations ([Sutcliffe et al., 2007](#); [Chao et al., 2010](#)) for all alcoholic beverages. Most studies collected data on consumption of alcoholic beverages only at baseline. Two studies examined lifetime alcohol

use up to baseline ([Rohrmann et al., 2008](#)) and another alcohol use at ages 18 and 45 ([Velicer et al., 2006](#)) and did not find associations.

2.12.2 Cohort studies in special populations

Two of the nine studies of special populations showed an association between alcoholic beverage consumption and cancer of the prostate. [Tønnesen et al. \(1994\)](#) and more recently [Thygesen et al. \(2009\)](#) (Table 2.55 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.55.pdf>) studying Danish alcohol abusers observed greater numbers of cancers of the prostate compared with the number expected from the general population. None of the studies provided information on individual exposures or adjusted for potential confounders.

2.12.3 Case–control studies

Studies published since [IARC \(2010\)](#) are summarized in Table 2.56 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.56.pdf>. Six of the 38 case–control studies considered aggressiveness of disease. In the study of [Walker et al. \(1992\)](#), 90% of the cases were advanced at presentation, and in the study by [Li et al. \(2008b\)](#), almost 50% of the cases were advanced and about 40% of moderately differentiated tumour presentation. The majority of the studies showed no association between consumption of alcoholic beverages and cancer of the prostate. Six studies found a positive association ([De Stefani et al., 1995](#); [Hayes et al., 1996](#); [Sharpe & Siemiatycki, 2001](#); [Chang et al., 2005](#); [Gallus et al., 2007](#); [Benedetti et al., 2009](#)). [De Stefani et al., \(1995\)](#) found a borderline elevation of risk for high levels of consumption of beer, but the risk at high levels of total alcohol consumption was not significantly elevated. [Hayes et al. \(1996\)](#) found significant elevations in risk for ‘heavy’ and ‘very heavy’ consumers of alcoholic beverages, with higher risks among

those with poorly or undifferentiated tumours, or with regional or distant metastases. [Sharpe & Siemiatycki \(2001\)](#) reported an elevation in risk for those with long duration of drinking, with the greatest elevation in risk for those who started drinking at age < 15 years. An elevated risk with increasing drink/year [with close to significant trend] was reported by [Benedetti et al. \(2009\)](#) among beer drinkers, as well as a borderline increased risk among moderate red wine drinkers. [Gallus et al. \(2007\)](#) reported an increased risk among men with poorly differentiated tumours (Gleason score ≥ 7). This association was not significant for all cancers of the prostate combined (regardless of the stage/differentiation status). [Chang et al. \(2005\)](#) found an association between consumption of alcoholic beverages (in g/week) and risk of cancer of the prostate with a borderline trend; there was no association with advanced cancer, whereas localized cancer showed significant association but without a dose–response relationship. [De Stefani et al. \(2009\)](#) analysed dietary patterns consisting of alcoholic beverages and processed meat and found no significant association with cancer of the prostate.

2.12.4 Meta-analyses

A meta-analysis that included six cohort and 27 case–control studies that were reported before July 1998 resulted in a relative risk estimate of 1.05 (95%CI: 0.98–1.11) for ever consumption of alcoholic beverages and of 1.05 (95%CI: 0.91–1.20) for each additional drink of alcohol per day ([Dennis, 2000](#)). The latter estimate was based on 15 studies reporting amount of alcohol consumed. Based on these 15 studies, the estimated relative risk for 4 drinks/day was 1.21 (95%CI: 1.05–1.39) (Table 2.57 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.57.pdf>). [Middleton-Fillmore et al. \(2009\)](#) conducted a meta-analysis in which 14 cohorts and 21 case–control studies were included, reporting a

weak but statistically significant association of incidence of cancer of the prostate with alcohol consumption levels in population case–control studies (RR, 1.24; 95%CI: 1.14–1.34), but meta-analyses of 7 hospital-based case–control studies and 14 cohort studies found no associations between consumption of alcoholic beverages and cancer of the prostate.

2.13 Cancer of the kidney

In the previous *IARC Monograph* ([IARC, 2010](#)) it was concluded that both cohort and case–control studies provide consistent evidence of no increase in risk for cancer of the kidney with consumption of alcoholic beverages ([IARC, 2010](#)). In several studies, increasing intake of alcoholic beverages was associated with a significantly lower risk for cancer of the kidney. These inverse trends were observed in both men and women and with multiple types of alcoholic beverage.

Since [IARC \(2010\)](#), one cohort (Table 2.58 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.58.pdf>) and three case–control studies (Table 2.59 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.59.pdf>) have been identified.

[Allen et al. \(2009\)](#) reported a decrease in risk for cancer of the kidney associated with moderate alcohol intake in women. The relative risk associated with ≥ 15 drinks per week was 0.66 (95%CI: 0.48–0.92); the reduction in risk per 10 g alcohol/day was 12% (95%CI: 1% to 22%).

[Greving et al. \(2007\)](#) (855 cases) reported an inverse association between alcohol intake measured as gram of ethanol per month and cancer of the kidney. [Pelucchi et al. \(2008\)](#) (1534 cases), in an update of a previous study ([Pelucchi et al. \(2002\)](#)) together with a new study from the same area, found an inverse association between total alcohol intake or intake of wine measured as drinks per day and cancer of the kidney;

however, they did not find any effect of duration (years) of drinking or age of starting. [Benedetti et al. \(2009\)](#) (156 cases) found no effect of alcohol intake on the risk of cancer of the kidney.

2.14 Cancer of the urinary bladder

In the previous *IARC Monograph* ([IARC, 2010](#)) it was concluded that the evidence for an association between consumption of alcoholic beverages and risk for cancer of the urinary bladder was inconsistent.

One cohort ([Allen et al., 2009](#)) and three case–control studies ([Cao et al., 2005](#); [Jiang et al., 2007](#); [Zaridze et al., 2009](#)) on the general population and one cohort study on alcoholics ([Thygesen et al., 2009](#)) have been identified since *IARC (2010)*.

[Allen et al. \(2009\)](#) found no association between consumption of alcoholic beverages and cancer of the urinary bladder in women (Table 2.60 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.60.pdf>). Likewise, [Thygesen et al. \(2009\)](#) reported no effect of alcohol on cancer of the urinary bladder among alcoholics (Table 2.61 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.61.pdf>).

Two of the case–control studies ([Cao et al., 2005](#); [Zaridze et al., 2009](#)) found no consistent association between consumption of alcoholic beverages and risk for cancer of the urinary bladder (Table 2.62 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.62.pdf>). However, [Jiang et al. \(2007\)](#) in a large case–control study (1671 cases) found a statistically significant reduced risk both in relation to frequency of alcohol intake, duration (in years), and age of initiation. The reduction in risk was particularly large among those who urinated frequently. [The reduced risk for cancer of the urinary bladder among those who urinated frequently may to some extent be due

to a high liquid intake and dilution of potential carcinogens.]

2.15 Cancers of the lymphatic and haematopoietic system

Lymphomas and haematopoietic malignancies comprise a heterogeneous group of malignancies and their respective etiologies are not fully understood. In the previous *IARC Monograph* ([IARC, 2010](#)) it was concluded that there was *evidence suggesting lack of carcinogenicity* in humans for alcoholic beverages and non-Hodgkin lymphoma (NHL). The results of cohort studies and evidence from some very large case–control studies showed an inverse association or no association between the consumption of alcoholic beverages and the risk for NHL. In general, there was no evidence of substantial differences in the effect of specific beverage types or for specific histological subtypes of NHL. The evidence for an association between consumption of alcoholic beverages and risk for Hodgkin disease was sparse, and no consistent pattern of association was observed for leukaemia and multiple myeloma ([IARC, 2010](#)).

2.15.1 Cohort studies in the general population

In seven cohort studies, associations of consumption of alcoholic beverages and the risk for lymphatic and/or haematopoietic cancers were examined ([Boffetta et al., 1989](#); [Kato et al., 1992](#); [Chiu et al., 1999](#); [Lim et al., 2006](#); [Lim et al., 2007](#); [Allen et al., 2009](#); [Klatsky et al., 2009](#)). Studies published since the previous Monograph ([IARC, 2010](#)) are summarized in Table 2.63 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.63.pdf>)

For NHL specifically, [Chiu et al. \(1999\)](#) found a non-significant inverse association with consumption of alcoholic beverages among postmenopausal women in the USA. This relationship

persisted after adjustment for several potential confounding factors including age, total energy intake, residence (farm, no farm), education, marital status, history of transfusion and diabetes, and intake of red meat and fruit. [The Working Group noted that the level of alcohol intake was very low in this study.] [Lim et al. \(2006\)](#) found weak evidence of an inverse association among Finnish male smokers in a multivariate analysis. The three cohort studies published recently and conducted among retired persons in the USA ([Lim et al., 2007](#)), among middle-aged women in the United Kingdom ([Allen et al., 2009](#)), and in a multiethnic USA population ([Klatsky et al., 2009](#)) have shown significantly decreased risk of NHL among people with moderate alcohol intake. A borderline significant inverse association was also shown for consumers of 7 or more drinks per week who were diagnosed with B-cell lymphoma, chronic lymphocytic lymphoma or small lymphocytic lymphoma, as well as an inverse (although non-significant) association of Hodgkin lymphoma risk with consumption of alcoholic beverages ([Lim et al., 2007](#)).

In a study among American men of Japanese ancestry that also considered several potential lifestyle, medical and dietary confounding factors, consumption of ≥ 30 ml alcohol per day compared with non-drinkers was associated with a threefold higher risk for lymphoma and leukaemia combined ([Kato et al., 1992](#)). In the multiethnic cohort in the USA ([Klatsky et al., 2009](#)) risk for myelocytic leukaemia among regular drinkers compared with never-drinkers plus those reporting < 1 drink/month, and risk for lymphocytic leukaemia among people drinking more than 2 drinks per week versus drinkers who drank < 1 drink/week showed inverse associations (p for trend 0.01 and 0.03, respectively). [Allen et al. \(2009\)](#) did not find any association between alcohol intake and risk of all leukaemias combined.

In the four cohort studies that assessed consumption of alcoholic beverages and the risk

for multiple myeloma, no association was found in three ([Lim et al., 2006](#); [Allen et al., 2009](#); [Klatsky et al., 2009](#)) and in one a lower risk among ever regular drinkers compared with never regular drinkers was found ([Boffetta et al., 1989](#)).

2.15.2 Cohort studies in special populations

Five studies among heavy alcoholic beverage users or brewery workers have investigated the risk for lymphatic and/or haematopoietic cancers ([Hakulinen et al., 1974](#); [Jensen, 1979](#); [Robinette et al., 1979](#); [Schmidt & Popham, 1981](#); [Carstensen et al., 1990](#)).

Three studies examined lymphatic and haematopoietic cancers combined ([Jensen, 1979](#); [Robinette et al., 1979](#); [Carstensen et al., 1990](#)), [Jensen \(1979\)](#) found no significant differences between the observed number of cases among Danish brewery workers compared with the expected number of cases computed from age-, sex-, and area-specific rates. [Carstensen et al. \(1990\)](#) found slightly increased risk for these cancers among Swedish brewery workers compared to the expected cases calculated using age, follow-up time, and area-standardized rates of the Swedish male population. [Robinette et al. \(1979\)](#) found a non-significant decreased risk among chronic alcoholic male USA veterans compared with expected numbers computed from age- and time-specific rates for the US male population.

In two studies, the observed number of cases of lymphoma among alcoholics was lower than that expected based on rates for the local population ([Hakulinen et al., 1974](#); [Schmidt & Popham, 1981](#)).

In studies among alcoholics, the observed number of cases of leukaemia did not differ significantly from those expected in one study ([Hakulinen et al., 1974](#)), and was non-significantly lower in two other studies ([Robinette et al., 1979](#); [Schmidt & Popham, 1981](#)). In studies among brewery workers, [Jensen \(1979\)](#) found

no significant difference between the observed and expected number of leukaemia deaths, while [Carstensen *et al.* \(1990\)](#) found a 1.6-fold higher risk of mortality among brewery workers compared with those expected from the local population.

2.15.3 Case–control studies

(a) Lymphomas

Associations between consumption of alcoholic beverages and the risk for lymphoma were evaluated in 22 case–control studies ([Williams & Horm, 1977](#); [Cartwright *et al.*, 1988](#); [Brown *et al.*, 1992](#); [Nelson *et al.*, 1997](#); [Tavani *et al.*, 1997](#); [De Stefani *et al.*, 1998](#); [Matsuo *et al.*, 2001a](#); [Tavani *et al.*, 2001b](#); [Briggs *et al.*, 2002](#); [Chiu *et al.*, 2002](#); [Morton *et al.*, 2003](#); [Chang *et al.*, 2004](#); [Willett *et al.*, 2004](#); [Besson *et al.*, 2006a, b](#); [Nieters *et al.*, 2006](#); [Deandrea *et al.*, 2007](#); [Casey *et al.*, 2007](#); [Gorini *et al.*, 2007b](#); [Willett *et al.*, 2007](#); [Monnereau *et al.*, 2008](#); [Benedetti *et al.*, 2009](#)). Studies published since the previous Monograph ([IARC, 2010](#)) are summarized in Table 2.64 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.64.pdf>).

Most case–control studies of consumption of alcoholic beverages and lymphoma focused specifically on NHL and/or its histological subtypes. [Chang *et al.* \(2004\)](#) found no overall association of NHL risk with moderate consumption of alcoholic beverages, although there was a suggestive possible increased risk of NHL among men. In that study, all cases and controls were free of human immunodeficiency viral infection and several potential confounding factors including age, tobacco smoking and occupational exposure to pesticides were considered. [Briggs *et al.* \(2002\)](#) also found no difference in the risk for NHL between drinkers and non-drinkers after adjustment for age, ethnicity and smoking status. [Casey *et al.* \(2007\)](#) found no significant associations of different characteristics of consumption of alcoholic beverages considering drinkers versus

non drinkers, current and former drinking, age at drinking debut, drinking duration or daily intake for all lymphoid neoplasms and B-cell lymphomas. An inverse association for ever alcohol drinking and NHL was observed in a large multicentric study ([Monnereau *et al.*, 2008](#)) with 399 NHL cases (OR, 0.7; 95%CI: 0.5–1.0).

Most individual studies of NHL have limited power to conduct detailed analyses of consumption of alcoholic beverages and risk for this disease, particularly for specific beverage types and histological subtypes. Therefore, data from nine case–control studies conducted in Italy, Sweden, the United Kingdom and the USA were pooled to include 6492 cases of NHL and 8683 controls ([Morton *et al.*, 2005](#)). The analysis showed a significantly lower risk for NHL for ever drinkers when compared to non-drinkers; however, there was no consistent dose–response relationship between risk and frequency of consumption of alcoholic beverages, duration of alcoholic beverage consumption or age at starting drinking. The risk for NHL for current drinkers was lower than that for former drinkers. There was no difference in association by alcoholic beverage type or for the combination of beverages types consumed. For specific subtypes of NHL, no significantly elevated risks were found. The lowest risk associated with ever drinking versus non-drinker was that for Burkitt lymphoma (OR, 0.51; 95%CI: 0.33–0.77). Low risks for diffuse B-cell, follicular and T-cell lymphomas associated with ever drinking were also noted. The findings were unchanged when the analyses were restricted to studies that had a high response rate.

A multicentre case–control study of NHL and consumption of alcoholic beverages included data from five European countries and comprised 1742 cases and 2465 controls ([Besson *et al.*, 2006a](#)). Overall, there were no associations observed for ever drinking, age at starting drinking, duration of drinking or monthly consumption with risk for all NHL or with any

histological subtype; similarly, no associations with risk of NHL were found with any specific type of alcoholic beverage. However, a lower risk associated with regular alcoholic beverage intake was observed for men (OR, 0.76; 95%CI: 0.62–0.93; 691 exposed cases) and for non-Mediterranean countries (OR, 0.73; 95%CI: 0.61–0.86).

Among the nine studies that examined Hodgkin lymphoma specifically ([Williams & Horm, 1977](#); [Tavani et al., 1997](#); [Besson et al., 2006b](#); [Nieters et al., 2006](#); [Deandrea et al., 2007](#); [Gorini et al., 2007b](#); [Willett et al., 2007](#); [Monnereau et al., 2008](#); [Benedetti et al., 2009](#)), a consistent inverse association was found almost in all. In the large multicentre European study, the odds ratio for Hodgkin lymphoma associated with ever regular drinking compared with never regular drinking was 0.61 (95%CI: 0.43–0.87; 81 exposed cases); this association was consistent for younger and older adults ([Besson et al., 2006b](#)). Other multicentre studies have also shown an inverse association of Hodgkin lymphoma risk and frequent alcohol consumption of the order of 0.50 ([Gorini et al., 2007b](#); [Monnereau et al., 2008](#)). [Willett et al. \(2007\)](#) found that the risk of Hodgkin lymphoma was higher among non-drinkers and persons with low alcohol consumption.

Inverse associations were also observed between specific alcoholic beverage types, namely wine and aperitif, and Hodgkin lymphoma ([Gorini et al., 2007b](#); [Monnereau et al., 2008](#)).

(b) Leukaemia

The association of consumption of alcoholic beverages with risk for adult leukaemia was examined in eight case–control studies ([Williams & Horm, 1977](#); [Brown et al., 1992](#); [Wakabayashi et al., 1994](#); [Chang et al., 2004](#); [Pogoda et al., 2004](#); [Rauscher et al., 2004](#); [Gorini et al., 2007a](#); [Monnereau et al., 2008](#)). Studies published since the previous Monograph are summarized in Table 2.65 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.65.pdf>).

No consistent patterns of associations between total consumption of alcoholic beverages and risk for all leukaemias combined were observed. In two studies a non-significant two- to threefold higher risk for acute lymphocytic leukaemia associated with heavy drinking ([Wakabayashi et al., 1994](#)) or with any drinking ([Brown et al., 1992](#)) was found, while in another no association of drinking with risk for this type of leukaemia was found ([Gorini et al., 2007a](#)). Similarly, there was no consistent evidence of associations with acute non-lymphocytic leukaemia, chronic lymphocytic leukaemia or chronic myeloid leukaemia in these studies. [Chang et al. \(2004\)](#) found a positive significant association between high wine intake and risk for chronic lymphocytic leukaemia.

(c) Multiple myeloma

Associations between consumption of alcoholic beverages and the risk for multiple myeloma were examined in nine case–control studies, five in the USA, one in Canada, two in Italy and one in France ([Williams & Horm, 1977](#); [Gallagher et al., 1983](#); [Linnet et al., 1987](#); [Brown et al., 1992](#); [Brown et al., 1997](#); [Deandrea et al., 2007](#); [Gorini et al., 2007b](#); [Hosgood et al., 2007](#); [Monnereau et al., 2008](#)). Studies published since the previous Monograph are summarized in Table 2.66 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.66.pdf>). In the largest studies, there was a statistically significant lower risk for multiple myeloma among drinkers compared with non-drinkers in white men ([Hosgood et al., 2007](#)) and to a lesser extent in black men and white women ([Brown et al., 1997](#)) and among both men and women ([Gorini et al., 2007b](#)), but the latter associations were non-significant. [Brown et al. \(1997\)](#) found a non-significant 2.8-fold higher risk for multiple myeloma for white women who consumed ≥ 22 drinks per week. Non-significantly increased risk of multiple myeloma for consumption of alcoholic beverages was found by [Deandrea et al. \(2007\)](#)

and [Monnereau et al. \(2008\)](#) after adjustment for age, centre, sex and tobacco. No consistent association patterns were observed among the other case-control studies. Most studies collected data on alcoholic beverage consumption from proxy respondents, and some included prevalent cases. In addition, not all studies controlled for the potential confounding effects of tobacco smoking, and only two controlled for other factors such as farming, family history of cancer and occupational exposure to high-risk chemicals ([Brown et al., 1992](#); [Monnereau et al., 2008](#)).

2.16 Other cancers

In the previous *IARC Monograph* ([IARC, 2010](#)) it was noted that the evidence for an association of consumption of alcoholic beverages with risk of other female cancers (vulva and vagina) and cancers of the testis, brain, thyroid, and skin melanoma was generally sparse and/or inconsistent.

2.16.1 Cancers of the vulva and vagina

In two cohort studies the association between consumption of alcoholic beverages and risk for other female cancers was examined. These were carried out in women being treated for alcohol abuse or alcoholism in Sweden ([Sigvardsson et al., 1996](#); [Weiderpass et al., 2001](#)). In one study an elevated risk for vaginal cancer but not for vulva cancer was found ([Weiderpass et al., 2001](#)). [Sigvardsson et al. \(1996\)](#) reported high relative risks for both vulva and vaginal cancers combined. In these studies relative risk estimates could not be adjusted for factors that may have confounded the association between alcoholic beverage consumption and vulva and vaginal cancers, such as HPV infections, number of sexual partners and tobacco smoking. It is possible that women who abuse alcohol have other behavioural patterns that may affect risks for these cancers.

Four case-control studies investigated the association between consumption of alcoholic beverages and risk for vulva cancer, conducted in Italy ([Parazzini et al., 1995b](#)) and in the USA ([Williams & Horm, 1977](#); [Mabuchi et al., 1985](#); [Sturgeon et al., 1991](#)); one study from Denmark ([Madsen et al., 2008](#)) investigated both cancer of the vulva and vagina. Studies published since the previous Monograph ([IARC, 2010](#)) are summarized in Table 2.67 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.67.pdf>. Three were hospital-based studies ([Williams & Horm, 1977](#); [Mabuchi et al., 1985](#); [Parazzini et al., 1995b](#)), one was population-based ([Sturgeon et al., 1991](#)), while [Madsen et al. \(2008\)](#) used two sets of controls, population- and hospital-based. Confounding factors were considered in four studies ([Williams & Horm, 1977](#); [Sturgeon et al., 1991](#); [Parazzini et al., 1995b](#); [Madsen et al., 2008](#)), but only two of these provided risk estimates adjusted for both smoking and sexual behaviour ([Sturgeon et al., 1991](#); [Madsen et al., 2008](#)). [Williams & Horm \(1977\)](#), [Mabuchi et al. \(1985\)](#), [Sturgeon et al. \(1991\)](#) and [Parazzini et al. \(1995b\)](#) reported no association between alcoholic beverage consumption and risk for vulva cancer. [Madsen et al. \(2008\)](#) found a higher risk among drinkers compared to non-drinkers, for both vaginal and vulva cancers.

There was no evidence of dose-response for consumption of alcoholic beverages and vulva cancer, in any of these studies, either in terms of frequency of alcohol consumption ([Parazzini et al., 1995b](#)), in terms of years of alcohol consumption ([Madsen et al., 2008](#)), or when providing two defined levels of alcohol consumption ([Williams & Horm, 1977](#)). [Williams & Horm \(1977\)](#), [Mabuchi et al. \(1985\)](#) and [Sturgeon et al. \(1991\)](#) investigated risk of vulva cancer in relation to consumption of different alcoholic beverages. No significant associations were found with any type of alcoholic beverage.

2.16.2 Other sites

No new studies have been identified for cancer of testis, one on brain cancer and thyroid cancer, and three on skin cancer (malignant melanoma, basal cell carcinoma and squamous cell carcinoma).

In a large cohort study of women in the United Kingdom ([Allen et al., 2009](#)) no association of consumption of alcoholic beverages was found with brain cancer (Table 2.68 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.68.pdf>), but a significant inverse association with thyroid cancer (Table 2.69 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.69.pdf>).

No association between consumption of alcoholic beverages and malignant melanomas was found by [Allen et al. \(2009\)](#) (Table 2.70 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.70.pdf>) or by [Benedetti et al. \(2009\)](#) in a case-control study (Table 2.71 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.71.pdf>). In a cohort study in Australia [Ansems et al. \(2008\)](#) found no significant association between overall basal cell carcinoma or squamous cell carcinoma risk and total alcohol intake or intake of beer, white wine, red wine or sherry and port (Table 2.70 on-line). Among those with a prior skin cancer history, there was a significant increase in risk of squamous cell carcinoma for above-median consumption of sherry and port compared with abstainers (multivariable adjusted RR, 2.46; 95%CI: 1.06–5.72).

2.17 Parental exposure and childhood cancers

Associations of paternal consumption of alcoholic beverages before pregnancy and/or maternal consumption of alcoholic beverages during pregnancy with risk for haematopoietic

cancers in children were examined in nine case-control studies in Australia, Canada, France, the Netherlands, the United Kingdom and the USA ([McKinney et al., 1987](#); [Severson et al., 1993](#); [van Duijn et al., 1994](#); [Shu et al., 1996](#); [Infante-Rivard et al., 2002](#); [Menegaux et al., 2005](#); [Menegaux et al., 2007](#); [MacArthur et al., 2008](#); [Rudant et al., 2008](#)). Studies published since the previous Monograph are summarized in Table 2.72 (available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.72.pdf>).

No association between maternal alcoholic beverage intake 1 month or 1 year before pregnancy with risk of any childhood leukaemia or lymphoma was reported by [Severson et al. \(1993\)](#), [Shu et al. \(1993\)](#) and [van Duijn et al. \(1994\)](#), whereas a borderline significant association for acute leukaemia and ALL was observed by [MacArthur et al. \(2008\)](#) and [Infante-Rivard et al. \(2002\)](#) found a positive association for ALL.

For maternal alcoholic beverage consumption during pregnancy, no association was found with leukaemia or lymphoma ([McKinney et al., 1987](#)) or with ALL ([Rudant et al., 2008](#)), while [Infante-Rivard et al. \(2002\)](#) found a reduced risk for ALL when comparing any intake with no intake. Statistically significant two- to 2.4-fold increased risk for acute non-lymphocytic leukaemia were associated with any maternal alcoholic beverage consumption during pregnancy in two studies ([van Duijn et al., 1994](#); [Menegaux et al., 2005](#)). Similarly, statistically significant positive associations between maternal alcoholic beverage consumption and risk for ALL ([Shu et al., 1993](#); [Menegaux et al., 2005, 2007](#); [MacArthur et al., 2008](#)) and acute myeloid leukaemia ([Severson et al., 1993](#); [Shu et al., 1993](#)) were observed. The strongest associations observed in the studies of alcoholic beverages and acute myeloid leukaemia were for children diagnosed at 10 years of age or younger ([Severson et al., 1993](#); [Shu et al., 1993](#)). Overall, there was no consistent evidence of dose-response relationships for maternal or

paternal alcoholic beverage intake or for intake of any specific type of alcohol beverage and risk for any childhood haematopoietic cancer. Most studies adjusted for potential confounding factors including maternal age, maternal smoking, and child's sex. Importantly, whether any of the observed associations between maternal or paternal consumption of alcoholic beverages and risk for childhood haematopoietic cancers are attributed to recall bias is unclear.

2.18 Polymorphisms and genetic susceptibility

Studies that identify associations between genetic polymorphisms and inter-individual differences in susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. If the polymorphism has been demonstrated experimentally to modify the functional activity of the gene product in a manner that is consistent with increased susceptibility, these data may be useful in making causal inferences. Similarly, studies that measure cell functions, enzymes or metabolites that are thought to be the basis of susceptibility may provide evidence that reinforces biological plausibility. If the known phenotype of a genetic polymorphism can explain the carcinogenic mechanism of the agent being evaluated, data on this phenotype may be useful in making causal inferences.

However, when data on genetic susceptibility originate from multiple comparisons in subgroup analyses, false-positive results and inconsistencies across studies can be generated. Furthermore, many of the identified susceptibility genes have no or unknown functional characterization; only for a few genes (e.g. ALDH2) are functional studies available; and generally induction of enzymes is not considered. Such data therefore require careful evaluation.

A challenge in the interpretation of the associations between the polymorphisms affecting alcohol and/or acetaldehyde metabolism and cancer is that the genes coding for more active alcohol oxidizing enzyme and/or less active acetaldehyde oxidizing enzyme, may both promote and inhibit the development of cancer. Carriers of genes enhancing alcohol oxidation and/or inhibiting acetaldehyde oxidation on average consume less alcohol ([Matsuo *et al.*, 2006b, 2007](#); [Zintzaras *et al.*, 2006](#)) and thus may be protected from harmful chronic effects (e.g. cancer) induced by alcohol unless they drink heavily. Thus, in studying the mechanisms of the associations between these polymorphisms and cancer, it is essential to control for differences in alcohol drinking.

2.18.1 Alcohol dehydrogenase-1B (ADH1B)

ADH1B (previously called *ADH2*) is polymorphic, and its superactive *ADH1B*2* allele is highly prevalent among East Asians (54–96%; [Goedde *et al.*, 1992](#)), but relatively rare among Caucasians (1–23%). Individuals with the *ADH1B*1/*1* genotype code less active ADH, which is a risk factor for excessive alcohol consumption in both East Asians and Caucasians ([Zintzaras *et al.*, 2006](#); [Matsuo *et al.*, 2007](#)).

(a) Cancer of the oesophagus

Individuals with the *ADH1B*1/*1* genotype were at increased risk for oesophageal cancer in 15 case–control studies among several populations ([Hori *et al.*, 1997](#); [Yokoyama *et al.*, 1998](#); [Chao *et al.*, 2000](#); [Matsuo *et al.*, 2001b](#); [Yokoyama *et al.*, 2001, 2002](#); [Boonyaphiphat *et al.*, 2002](#); [Yang *et al.*, 2005](#); [Yang *et al.*, 2007](#); [Guo *et al.*, 2008](#); [Hashibe *et al.*, 2008](#); [Lee *et al.*, 2008b](#); [Cui *et al.*, 2009](#); [Ding *et al.*, 2009](#)) and in a cohort study in cancer-free Japanese alcoholics ([Yokoyama *et al.*, 2006b](#)) ([Tables 2.73, 2.74](#)). The difference was not significant in two Japanese studies ([Tanabe *et al.*, 1999](#); [Yokoyama *et al.*, 2006a](#)) and one study in South

Africa ([Li et al., 2008a](#)). [Many studies did not control for the amount of alcohol consumption, which makes it difficult to make firm conclusions about the etiology of the *ADH1B**1/*1 associated cancers.]

(b) *Upper aerodigestive tract cancers combined*

In four Japanese studies ([Yokoyama et al., 2001, 2006b](#); [Asakage et al., 2007](#); [Hiraki et al., 2007](#)), one European study ([Hashibe et al., 2006](#)) and one Indian study ([Solomon et al., 2008](#)) an *ADH1B**1/*1-associated increased risk for upper aerodigestive tract cancers was found in alcohol drinkers. No significant association was found in another European study ([Risch et al., 2003](#); [Tables 2.74, 2.75](#)).

A recent large multicentre study from Europe and Latin America of *ADH* genes and UADT cancer that focused on seven separate *ADH* variants known to change an amino acid (missense substitution) included a total of 3800 cases and 5200 controls ([Hashibe et al., 2008](#)). One variant in *ADH1B* (rs1229984) that codes for fast ethanol metabolism was associated with a strong decreased risk for UADT cancer, after adjusting for amount of alcohol consumed (OR for dominant model, 0.56; 95%CI: 0.47–0.66; $P = 4 \times 10^{-11}$). The odds ratio was 0.45 (95%CI: 0.35–0.57) for oral/pharyngeal cancers combined and 0.71 (95%CI: 0.57–0.88) for laryngeal cancer.

(c) *Cancers of the stomach, colorectum and pancreas*

One Polish study showed no significant effects of the *ADH1B* polymorphism on risk for cancer of the stomach ([Zhang et al., 2007b](#); Table 2.76 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.76.pdf>). For cancer of the colorectum, two Japanese case-control studies of alcohol drinkers found an increased risk in *ADH1B**1/*1 subjects compared with *ADH1B**2 carriers without stratification of *ALDH2* genotypes ([Matsuo et al., 2006a](#); [Yin et al., 2007](#)). However, stratification by *ALDH2*

genotypes rendered the association opposite within the *ALDH2**1/*1 subjects in one of the studies ([Matsuo et al., 2006a](#)), while no such effect was seen in the other study ([Yin et al., 2007](#)). In a Chinese study the *ADH1B**2/*2 genotype tended to increase the risk for cancer of the colorectum regardless of the *ALDH2* genotype ([Gao et al., 2008](#)). Also, a study in Spain reported a non-significant decrease in risk for cancer of the colorectum for the *ADH1B**2/*2 versus *ADH1B**1/*1 ([Landi et al., 2005](#)).

The *ADH1B**2 allele has been associated with an increase in risk for cancer of the pancreas and consumption of alcoholic beverages among Japanese ([Kanda et al., 2009](#)).

(d) *Hepatocellular cancer*

In two studies in Japan and in a study in China it was concluded that the *ADH1B* polymorphism had no significant impact on the risk for hepatocellular carcinoma ([Takeshita et al., 2000b](#); [Sakamoto et al., 2006](#); [Ding et al., 2008](#); Table 2.76 on-line).

(e) *Cancer of the breast*

In a study in Germany ([Lilla et al., 2005](#)), a decreased risk for cancer of the breast with consumption of alcoholic beverages ≥ 12 g ethanol/day compared with no intake was observed in women with the *ADH1B**2 allele, whereas no such association was found in women with the *ADH1B**1/*1 genotype. In four other studies from Japan, United Kingdom and the USA, no significant differences in the risk by *ADH1B* polymorphism were observed ([Cox et al., 2007](#); [Terry et al., 2007b](#); [Visvanathan et al., 2007](#); [Kawase et al., 2009](#); Table 2.76 on-line).

2.18.2 *ADH1C*

ADH1C (previously called *ADH3*) is a major gene polymorphism among Caucasians. The homodimer encoded by the *ADH1C**1 allele catalyses the production of acetaldehyde

Table 2.73 Case-control studies and meta-analyses of *ALDH2*, *ADH1B* and *ADH1C* genotype-associated risk for cancer of the oesophagus

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ¹	Comments	
Hori et al. (1997) , Tokyo, Japan, study period NR	Squamous cell carcinoma	<i>ALDH2</i> *1/*1	20	1.0	No adjustment was reported	
			*1/*2	70		4.4 (2.5–7.7)
			*2/*2	3		0.9 (0.2–3.6)
		<i>ADH1B</i> *2/*2	40	1.0		
			*1/*2	33		1.7 (0.9–3.0)
			*1/*1	21		6.2 (2.6–14.7)
Yokoyama et al. (1998) , Kanagawa, Japan, 1987–97	Oesophagus NOS	<i>ALDH2</i> *1/*1	41	1.00	Male alcoholics; because the differences in odds ratio between the incident cases and the prevalent cases were slight, the cases were combined. Adjusted for age, alcohol drinking and cigarette smoking. Possible partial overlap with Yokoyama et al. (2001)	
			*1/*2	46		12.50 (7.23–21.61)
Tanabe et al. (1999) , Hokkaido, Japan, 1994–97	Squamous cell carcinoma	<i>ALDH2</i> *1/*1	8	NS	Alcohol consumption and smoking did not differ between the cases and controls.	
			*1/*2	11		
			*2/*2	0		
Chao et al. (2000) , Taipei, Taiwan, China, 1997–99	Oesophagus	<i>ALDH2</i> *1/*1	22	Allele *2 was associated with risk ($P < 0.001$) Allele *1 was associated with risk ($P < 0.025$) No significant difference in prevalence of alleles in alcoholics with different diseases and between alcoholic and non-alcoholic oesophageal cancer cases	Alcoholics and non-alcoholic oesophageal cancer cases and alcoholic and non-alcoholic controls. No adjustment	
			*1/*2			37
			*2/*2			0
		<i>ADH1B</i> *1/*1	17			
			*1/*2			26
			*2/*2			16
		<i>ADH1C</i> *1/*1	38			
			*1/*2			21
			*2/*2			0

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ¹	Comments
Matsuo et al. (2001b) , Aichi, Japan, 1999–2000 (cases were first diagnosed as having esophageal cancer between 1984–2000 and visited the study centre in 1999–2000)	Oesophagus NOS	ALDH2			Adjusted for age, sex, drinking, smoking. Heavy drinkers defined as those drinking 75 mL ethanol/d, ≥ 5 d/wk. “Other participants” refers to those who were not heavy drinker
		All participants	35	1.00	
		*1/*1			
		*1/*2	66	3.72 (1.88–7.36)	
		*2/*2	1	0.80 (0.09–6.88)	
		Heavy drinkers			
		*1/*1	22	1.00	
		*1/*2	46	16.4 (4.41–61.2)	
		*2/*2	0	–	
		Other participants			
Yokoyama et al. (2001) , Kanagawa, Japan, 1993–2000	Squamous cell carcinoma	ALDH2			Male alcoholics. Adjusted for age, drinking, smoking, <i>ALDH2</i> and <i>ADH1B</i> genotypes. Possible partial overlap with Yokoyama et al. (1998)
		*1/*1	50	1.00	
		*1/*2	62	13.50 (8.06–22.60)	
		ADH1B			
		*1/*2 + *2/*2	56	1.00	
		*1/*1	56	2.64 (1.62–4.31)	

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ^a	Comments
Boonyaphiphat et al. (2002) , Songkhla, Thailand, 1997–2000	Squamous cell carcinoma	By alcohol intake			Unlike Japanese and Chinese studies, frequency of inactive <i>ALDH2</i> is low in the Thais; 20% in cases, 18% in controls. Adjusted for age, sex, smoking, betel chewing (drinking, <i>ALDH2</i> and <i>ADH1B</i> genotypes for overall)
		<i>ALDH2</i>			
		Non-drinker	40	1.00	
		*1/*1	12	1.56 (0.65–3.70)	
		*1/*2	42	2.16 (1.11–4.21)	
		≤ 60 g/d	8	2.52 (0.85–7.46)	
		*1/*2	79	5.28 (2.70–10.32)	
		> 60 g/d	20	10.83 (3.37–34.69)	
		*1/*1		Interaction <i>P</i> = 0.031	
		*1/*2			
Itoga et al. (2002) , Chiba, Japan [study period NR]	Oesophagus NOS	<i>ADH1B</i>			No adjustment was reported
		Non-drinker	35	1.00	
		*1/*2	18	0.89 (0.41–1.93)	
		*1/*1	28	2.00 (0.97–4.11)	
		≤ 60 g/d	22	2.34 (1.06–5.11)	
		*1/*2	38	3.35 (1.50–7.02)	
		> 60 g/d	61	11.46 (5.16–25.45)	
		*1/*1		Interaction <i>P</i> = 0.064	
		*1/*2			
		Habitual drinkers	47	1.0	
<i>ALDH2</i> *1	18	4.9 (<i>P</i> < 0.0001)			
<i>ALDH2</i> *2					
Watanabe et al. (2002) , Kagawa, Japan, 1998–2001	Squamous cell carcinoma	<i>ALDH2</i>			Prevalence of *2 allele was significantly higher in cases than in controls.
		*1/*1	10	See comments	
		*1/*2	18		
		*2/*2	1		

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ¹	Comments
Yokoyama et al. (2002) , Tokyo, Chiba, Kanagawa, Osaka, Japan, 2000–01	Squamous cell carcinoma	By alcohol intake ALDH2 *1/*1			Only male participants. Multivariate odds ratio of <i>ALDH2</i> *2/*2 in comparison with <i>ALDH2</i> *1/*1 was 7.83 (1.33–46.08). However, most men with *2/*2 genotype drank rarely or never and the risk was evaluated based on a small sample size (2 cases/43 controls).
		< 22 g/wk	0	0.0 (not calculable)	
		22–197 g/wk	3	1.00	
		198–395 g/wk	23	5.58 (1.54–20.25)	For <i>ADH1C</i> genotype the relative risk was associated with less active <i>ADH1C</i> *1/*1 versus active *1/*2 or *2/*2. When the linkage disequilibrium between <i>ADH1B</i> and <i>ADH1C</i> was taken into consideration, the <i>ADH1C</i> genotype did not significantly affect the risk for cancer.
		≥ 396 g/wk	33	10.38 (2.85–37.84)	
		Former drinker	4	8.81 (1.53–50.76)	
		*1/*2			
		< 22 g/wk	3	0.75 (0.14–4.11)	
		22–197 g/wk	21	5.82 (1.59–21.38)	
		198–395 g/wk	63	55.84 (15.40–202.51)	
		≥ 396 g/wk	73	88.88 (23.97–329.57)	Adjusted for age, strong alcoholic beverage, green-yellow vegetables and fruit (and alcohol drinking, <i>ALDH2</i> , <i>ADH1B</i> and <i>ADH1C</i> genotypes for overall association). Cases included in Yokoyama et al. (2001) were excluded from this study.
		Former drinker	9	50.50 (9.18–277.95)	
		*2/*2			
		< 22 g/wk	2	1.44 (0.22–9.54)	
		ADH1B			
		*1/*2 or *2/*2			
		< 22 g/wk	4	0.21 (0.06–0.68)	
		22–197 g/wk	20	1.00	
		198–395 g/wk	68	4.09 (2.25–7.42)	
		≥ 396 g/wk	80	7.01 (3.77–13.04)	
		Former drinker	11	5.73 (2.03–16.20)	
		*1/*1			

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ^a	Comments
Yokoyama <i>et al.</i> (2002) Contd.,	< 22 g/wk		1	4.25 (0.41–43.82)	
	22–197 g/wk		4	3.97 (1.01–15.63)	
	198–395 g/wk		18	33.30 (11.14–99.50)	
	≥ 396 g/wk		26	38.64 (13.27–112.55)	
	Former drinker		2	19.63 (1.65–233.20)	
	ADH1C				
	*1/*1				
	< 22 g/wk		5	0.23 (0.08–0.68)	
	22–197 g/wk		22	1.00	
	198–395 g/wk		69	3.66 (2.04–6.55)	
	≥ 396 g/wk		88	6.64 (3.66–12.05)	
	Former drinker		12	8.44 (2.94–24.25)	
	*1/*2 or *2/*2				
< 22 g/wk		0	Not calculable		
22–197 g/wk		2	0.81 (0.17–3.99)		
198–395 g/wk		17	13.32 (5.28–33.63)		
≥ 396 g/wk		18	23.83 (7.67–74.06)		
Former drinker		1	1.01 (0.09–11.93)		
Overall analyses	Oesophagus NOS				Results from overall analyses were adjusted for age, sex, smoking and alcohol drinking. Results by alcohol intake were adjusted for smoking. <i>P</i> for interaction between alcohol intake and genotypes for <i>ALDH2</i> was 0.03 for ≤ 250 g/wk and < 0.01 for > 250 g/wk alcohol intake. <i>P</i> for interaction for <i>ADH1B</i> was 0.24 for ≤ 250 g/wk and 0.32 for > 250 g/wk alcohol intake
ALDH2					
*1/*1				1.00	
*1/*2				6.43 (4.02–10.3)	
*2/*2				1.92 (0.23–15.7)	
ADH1B					
*2/*2				1.00	
*1/*2				1.57 (1.04–2.36)	
*1/*1				0.62 (0.22–1.72)	
By alcohol intake					
ALDH2					
*1/*1					

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ¹	Comments
Yang et al. (2005) , Contd.		Non drinker ≤ 250 g/wk > 250 g/wk *1/*2 Non-drinker ≤ 250 g/wk > 250 g/wk ADH1B *2/*2		1.00 1.88 (0.42–8.37) 4.62 (0.93–23.1)	
		Non-drinker ≤ 1200 g/yr ≥ 1200 g/yr *1/*2 or *1/*1 Non-drinker ≤ 1200 g/yr ≥ 1200 g/yr	38 126 1	1.00 5.03 (1.67–15.1) 25.8 (8.01–83.3)	
Cai et al. (2006) , Taixing, Jiangsu Province, China, 2000	Squamous cell carcinoma	ALDH2 *1/*1 *1/*2 *2/*2	119 61 25	1.00 0.76 (0.50–1.16) 1.72 (0.85–3.48)	Adjusted for age, sex, education level, body mass index, and history of smoking and alcohol drinking. An elevation of the risk for ESCC was pronounced most among carriers of <i>ALDH2</i> *2/*2 and <i>XRCC1</i> 399Gln/Gln or Gln/Arg who consumed a low level of dietary selenium (adjusted OR, 4.16; 95% CI: 1.14–15.12).

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ^a	Comments
Yokoyama et al. (2006a) , Tokyo, Chiba, Kanagawa, Osaka, Japan, 2000–04	Squamous cell carcinoma	By alcohol intake <i>ALDH2</i> *1/*1	12	1	Only female participants. Adjusted for age, smoking, green-yellow vegetables and fruit, hot food and beverages
		< 22 g/wk	5	0.80 (0.24–2.60)	
		22–197 g/wk	4	1.99 (0.52–7.68)	
		198–395 g/wk	4	3.16 (0.65–15.48)	
		≥ 396 g/wk			
		<i>ALDH2</i> *1/*2	8	0.5 (0.2–1.3)	
		< 22 g/wk	5	2.0 (0.5–7.1)	
		22–197 g/wk	2	4.7 (0.7–31)	
		198–395 g/wk	3	59 (4.7–750)	
		≥ 396 g/wk		NS	
		<i>ADH1B</i>			
Hashibe et al. (2006) , Romania, Poland, the Russian Federation, Slovakia, Czech Republic, 2000–02	Squamous cell carcinoma	<i>ADH1B</i> R48H	163	1.00	<i>ALDH2</i> +82A > G, +348C > T and –261C > T showed linkage disequilibrium and were associated with risk for oesophageal squamous-cell carcinoma.
		*1/*1	4	0.19 (0.07–0.53)	Adjusted for age, sex, country, yr of alcohol drinking, pack-yr of tobacco smoking.
		*1/*2 + *2/*2			
		<i>ADH1C</i> I350V	42	1.00	
		Ile/Ile (slow)	92	1.61 (1.07–2.43)	
		Ile/Val	30	1.74 (1.02–2.98)	
		Val/Val (fast; *1/*1)			
		<i>ADH1C</i> R272Q	42	1.00	
		Arg/Arg (slow)	88	1.62 (1.07–2.44)	
		Arg/Gln	30	2.03 (1.18–3.47)	
		Gln/Gln (fast; *1/*1)			
		<i>ALDH2</i> +82A			
		> G			

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ¹	Comments	
Hashibe et al. (2006) , Contd.	A/A		82	1.00		
	A/G		69	2.11 (1.46–3.05)		
	G/G		15	4.14 (2.03–8.46)		
	ALDH2 +348C					
	> T					
	T/T		83	1.00		
	T/C		71	2.29 (1.59–3.30)		
	C/C		12	3.71 (1.73–7.97)		
	ALDH2 –261C					
	> T					
Homann et al. (2006) , Germany, 1999–2003	T/T		85	1.00		
	T/C		71	2.32 (1.61–3.35)		
	C/C		12	3.85 (1.78–8.36)		
	ADH1C *1/*1 in heavy drinkers					
	Oesophagus NOS			2.93 (1.84–4.67)	Study participants were heavy alcohol drinkers: 123 oesophageal cancer cases and 525 controls with benign tumours. Adjusted for age, sex and smoking. [The reference group was not reported: ADH1C *2/*2 or ADH1C *2/*2 + ADH1C *1/*1.]	
	Yang et al. (2007) , Yanting, Sichuan Province, China, 2003–04	ADH1B *2/*2		37	1.0	Adjusted for age, sex, smoking, rapid food eating, quality of drinking-water, consumption of pickled vegetables and fresh fruits, vegetables and eggs. Non-drinkers also included ex-drinkers.
		Non-drinker		41	1.88 (0.86–4.15)	
		Current drinker *1/*2 or *1/*1		43	1.21 (0.63–2.33)	
		Non-drinker		70	3.94 (1.76–8.81)	
		Current drinker				
ALDH2 *1/*1						
Non-drinker			33	1.0		
Current drinker *1/*2 or *2/*2			57	3.15 (1.39–7.13)		
Non-drinker			47	2.03 (1.03–3.99)		
Current drinker			54	4.82 (2.06–11.27)		

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ^a	Comments		
Terry <i>et al.</i> (2007a), Connecticut, New Jersey and Washington, USA, 1993–95	Squamous cell carcinoma	ADH1C	4	1.0	Adjusted for age, gender and geographic site		
		*2/*2	10	1.0 (0.3–3.3)			
		*1/*2	9	1.7 (0.5–5.9)			
	Oesophageal and gastric cardia adenocarcinoma	ADH1C	17	1.0			
		*2/*2	52	1.2 (0.6–2.5)			
		*1/*2	45	2.0 (1.0–4.2)			
	Guo <i>et al.</i> (2008), Lanzhou, Gansu Province, China, 2004–07	Squamous cell carcinoma	ALDH2	37		1.00	Variables for which the results were adjusted were NR
			*1/*1	43		2.89 (1.11–5.64)	
			*1/*2	0		–	
			ADH1B	17		1.00	
*1/*1			25	3.67 (1.26–8.73)			
*2/*1			38	1.46 (0.71–2.59)			
*2/*2							
By alcohol intake							
ALDH2							
*1/*1			7	1.00			
0–200 g/wk	30	2.29 (0.91–5.57)					
> 200 g/wk							
*1/*2	7	0.56 (0.20–1.59)					
0–200 g/wk	36	8.58 (3.28–22.68)					
> 200 g/wk							
*2/*2	0	–					
0–200 g/wk							
ADH1B							
*1/*2 or *2/*2	13	1.00					
0–200 g/wk	50	4.75 (2.53–9.38)					
> 200 g/wk							
*1/*1	1	1.00 (0.18–9.22)					
0–200 g/wk	16	27.12 (8.52–70.19)					
> 200 g/wk							

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ¹	Comments
Lee <i>et al.</i> (2008b), Taipei and Kaohsiung, Taiwan, China, 2000–05	Squamous cell carcinoma	By alcohol intake			Adjusted for age, sex, study hospital, ethnicity, smoking, education, smoking, betel quid chewing, and consumption of fruits and vegetables. Another publication from this study (Lee <i>et al.</i> , 2009), reported that heterozygous ALDH2 increased the oesophageal cancer risk more prominently in younger population.
		<i>ALDH2</i>			
		*1/*1	17	1.0	
		Non-drinker	45	2.2 (1.1–4.5)	
		0.1–30 g/d	49	7.2 (3.3–15.9)	
		> 30 g/d			
		*1/*2			
		Non-drinker	38	1.1 (0.6–2.3)	
		0.1–30 g/d	114	14.5 (7.1–29.6)	
		> 30 g/d	129	102.6 (38.3–274.8)	
		*2/*2			
		Non-drinker	8	1.2 (0.4–3.4)	
		0.1–30 g/d	3	17.3 (1.4–213.7)	
		> 30 g/d	3	– (0 control subject)	
		<i>ADH1B</i>			
*2/*2					
Non-drinker	29	1.0			
0.1–30 g/d	58	3.5 (1.9–6.5)			
> 30 g/d	53	11.1 (5.0–24.4)			
*1/*2					
Non-drinker	26	0.8 (0.4–1.6)			
0.1–30 g/d	59	4.2 (2.2–7.9)			
> 30 g/d	64	14.2 (6.6–30.6)			
*1/*1					
Non-drinker	8	1.2 (0.4–3.6)			
0.1–30 g/d	45	10.6 (4.7–23.7)			
> 30 g/d	64	71.9 (22.6–228.5)			

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ^a	Comments
Ding <i>et al.</i> (2008), Taixing, Jiangsu Province, China, 2005–06	Oesophagus NOS	By alcohol intake			Adjusted for income
		ADH1B			
		Non-drinker			
		*2/*2	50	1.00	
		*1/*2	42	1.31 (0.70–2.46)	
		*1/*1	4	2.10 (0.35–12.54)	
		*1/*2 or *1/*1	46	1.37 (0.74–2.54)	
		Drinker			
		*2/*2	56	1.00	
		*1/*2	54	1.18 (0.64–2.16)	
*1/*1	15	2.90 (0.85–9.90)			
*1/*2 or *1/*1	69	1.36 (0.76–2.43)			
Li <i>et al.</i> (2008a), Cape Town, South Africa, 1997–2003	Squamous cell carcinoma	ALDH2			
		Non-drinker			
		*1/*1	26	1.00	
		*1/*2	43	1.29 (0.65–2.55)	
		*2/*2	27	4.67 (1.63–13.38)	
		*1/*2 or *2/*2	70	1.78 (0.94–3.37)	
		Drinker			
		*1/*1	64	1.00	
		*1/*2	46	2.47 (1.27–4.82)	
		*2/*2	15	8.63 (2.07–35.95)	
*1/*2 or *2/*2	61	3.08 (1.65–5.78)			
Li <i>et al.</i> (2008a), Cape Town, South Africa, 1997–2003	Squamous cell carcinoma	ADH1B			Results for participants from black racial groups (282 cases and 348 controls). All results for those with mixed ancestry (192 cases and 188 controls) were non-significant. Non-adjusted results.
		*1 allele	265	1.00	
		*2 allele	4	NS	
		*3 allele	13	NS	
		ADH1C			
		*1 allele	153	1.00	
		*2 allele	129	1.80 (P = 0.0004)	
ALDH2					
*1 allele	155	1.00			
*2 allele	27	2.35 (P = 0.008)			

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ¹	Comments
Hashibe et al. (2008) , Multicenter study (see Comments), 2000–05	Oesophagus	ADH1B *1/*1 *1/*2 or *2/*2 ADH1C G > A was in linkage disequilibrium with ADH1B	1	0.34 (0.20–0.56)	427 cases of oesophageal cancer. Pooled analysis of studies conducted in the Russian Federation (Moscow), Poland (Lodz), Romania (Bucharest), Czech Republic (Prague, Olomouc), Slovakia (Banska Bystrica), France (Paris), Greece (Athens), Italy (Aviano, Padova, Torino), Norway (Oslo), United Kingdom (Edinburgh, Manchester, Newcastle), Spain (Barcelona), Croatia (Zagreb), Cuba, Argentina (Buenos Aires) and Brazil (Goiania, Pelotas, Rio de Janeiro, Sao Paulo) Adjusted for age, sex, centre, cumulative alcohol consumption and smoking
Cui et al. (2009) , Japan (see Comments)	Squamous cell carcinoma	ALDH2 *1/*1 *1/*2 *2/*2 ADH1B *2/*2 *1/*2 *1/*1 By alcohol intake ALDH2 *2/*1 vs 1*1 + *2/*2 0–96.5 g/wk > 96.5 g/wk ADH1B *1/*1 vs *1/*2 + *2/*2 0–96.5 g/wk > 96.5 g/wk	314 735 17 510 363 194	1.00 3.48 (2.99–4.06) 0.47 (0.28–0.78) 1.00 1.17 (1.01–1.37) 4.10 (3.24–5.18) 3.35 (2.66–4.22) 6.20 (4.76–8.09) 3.18 (2.28–4.43) 4.74 (3.21–6.99)	Case samples ($n = 1070$) were from BioBank Japan, a collaborative network of 66 hospitals in Japan. Control samples in the first stage ($n = 938$) were obtained from volunteers in Osaka, Japan. The control groups for the second stage and replication analysis consisted of 1898 individuals who were registered in BioBank Japan as subjects with diseases other than cancers. Adjusted for age, gender, alcohol and smoking. Heterozygous ALDH2 increased the oesophageal cancer risk more prominently in younger population.

Table 2.73 (continued)

Reference, study location, period	Cancer site and/or type	Genes involved	No of cases/deaths	Relative risk (95% CI) ^a	Comments
Meta-analysis Lewis & Smith (2005)	Oesophagus NOS	<i>ALDH2</i> *1/*1 <i>ALDH2</i> *1/*2 <i>ALDH2</i> *2/*2		1.0 3.19 (1.86–5.47) 0.39 (0.16–0.80)	Meta-analysis of the studies: Hori et al. (1997) , Matsuo et al. (2001b) , Boonyaphiphat et al. (2002) , Itoga et al. (2002) , Yokoyama et al. (2002) . [Reduced risk with *2/*2 likely due to markedly lower levels of alcohol consumption in *2/*2 versus *1/*1 homozygotes.]

*ALDH2**1 is more active, *ADH1B**1 is less active, and *ADH1C**1 is more active alleles than the other allele in the respective genes.

ALDH, aldehyde dehydrogenase; *ADH*, alcohol dehydrogenase; CI, confidence interval; d, day or days; NOS, not otherwise specified; NR, not reported; NS, not significant; vs, versus; wk, week or weeks

Table 2.74 Cohort study of *ALDH2* and *ADH1B* genotype-associated risk for cancer of the oesophagus and upper aerodigestive tract

Reference, location	Cohort description	Exposure assessment	Cancer and site	Exposure categories	No. of subjects/ squamous-cell carcinoma	Hazard ratio (95% CI)	Adjustment factors	Comments
Yokoyama et al. (2006b) , Kanagawa, Japan	808 Japanese alcoholic men confirmed cancer-free by endoscopic screening during 1993–2005; endoscopic follow-up from 1 to 148 mo (median, 31 mo)	<i>ALDH2</i> , <i>ADH1B</i> genotyping at baseline examination in 556 patients	Upper aerodigestive tract squamous-cell carcinoma	<i>ALDH2</i> *1/*1 *1/*2 <i>ADH1B</i> *1/*2 + *2/*2 *1/*1	484/27 72/26 381/28 175/25	1 11.6 (5.7–23.3) 1 2.0 (1.02–4.0)	Age	
			Oesophageal squamous-cell carcinoma	<i>ALDH2</i> *1/*1 *1/*2 <i>ADH1B</i> *1/*2 + *2/*2 *1/*1	484/14 72/19 381/18 175/15	1 13.0 (5.2–32.1) 1 1.6 (0.7–3.9)		
			Oropharyngolaryngeal squamous-cell carcinoma	<i>ALDH2</i> *1/*1 *1/*2 <i>ADH1B</i> *1/*2 + *2/*2 *1/*1	484/17 72/13 381/16 175/14	1 11.7 (4.7–29.5) 1 2.0 (0.8–5.0)		

ADH, alcohol dehydrogenase; *ALDH*, aldehyde dehydrogenase; CI, confidence interval; mo, month or months

from ethanol at a rate 2.5 times faster than the homodimer encoded by the *ADH1C*2* allele ([Bosron & Li, 1986](#)).

(a) *Cancer of the oesophagus*

Associations between *ADH1C* genotype and oesophageal cancer have been investigated in five studies in populations mainly composed of Caucasians. A higher *ADH1C*1/*1*-associated risk was found in four ([Visapää et al., 2004](#); [Hashibe et al., 2006](#); [Homann et al., 2006](#); [Terry et al., 2007a](#); [Table 2.73](#)), in one of which all UADT cancers were combined ([Visapää et al., 2004](#); [Table 2.75](#)). However, no association was observed when the linkage disequilibrium between *ADH1B*2* and *ADH1C*1* was taken into consideration in one study ([Hashibe et al., 2006](#)). Both *ADH1B*2* and *ADH1C*1* were in linkage disequilibrium in an analysis by [Hashibe et al. \(2008\)](#).

In contrast to the overall direction in Caucasian populations, in two Japanese studies it was reported that the *ADH1C*2* allele increases the risk for oesophageal cancer ([Yokoyama et al., 2002](#); [Muto et al., 2005](#)). Again, when the linkage disequilibrium between *ADH1B* and *ADH1C* was taken into consideration, no relationship was found between *ADH1C* genotype and UADT cancer risk ([Yokoyama et al., 2002](#)). No significant associations were observed in a Chinese study ([Chao et al., 2000](#)). An association between *ADH1C*2* allele and risk of oesophageal cancer was reported in an African population ([Li et al., 2008a](#)).

(b) *Other upper aerodigestive tract cancers*

In six studies of Caucasians ([Coutelle et al., 1997](#); [Harty et al., 1997](#); [Homann et al., 2006](#); [Hashibe et al., 2006, 2008](#); [Arndt et al., 2008](#)) increased risk of other upper aerodigestive tract cancer cancers associated with the *ADH1C*1/*1* genotype was reported ([Table 2.75](#)). In two other studies of Caucasians ([Schwartz et al., 2001](#); [Peters et al., 2005](#)), two studies from Japan

and India ([Asakage et al., 2007](#); [Solomon et al., 2008](#)) and one Brazilian study of a mixed population ([Nishimoto et al., 2004](#)) opposite results were reported, with the *ADH1C*2/*2* genotype increasing the risk. When the linkage disequilibrium between *ADH1B* and *ADH1C* was taken into consideration ([Asakage et al., 2007](#)), no relationship was found between *ADH1C* genotype and cancer risk. No significant associations were observed in six other studies of Caucasians ([Bouchardy et al., 2000](#); [Olshan et al., 2001](#); [Sturgis et al., 2001](#); [Zavras et al., 2002](#); [Risch et al., 2003](#); [Wang et al., 2005](#)), or in a study of Japan ([Muto et al., 2005](#)).

(c) *Cancers of the stomach and colorectum*

In one study in the USA increased risk of gastric adenocarcinomas associated with the *ADH1C*1/*1* genotype was reported ([Terry et al., 2007a](#)) but in a Polish study no significant effects of the *ADH1C* polymorphism on stomach cancer risk was found ([Zhang et al., 2007b](#)) ([Table 2.76 on-line](#)).

Regarding the risk for cancer of the colorectum, in two European studies an increased risk in *ADH1C*1/*1* carriers compared with *ADH1C*2* subjects was found ([Tiemersma et al., 2003](#); [Homann et al., 2009](#)). However, an increased risk with *ADH1C*2/*2* genotype was reported in another study ([Giovannucci et al., 2003](#)). A trend with the *ADH1C*2/*2* genotype increasing the risk for cancer of the colorectum was also observed in another study of Caucasians [which was perhaps explained by higher alcohol consumption by those with **2/*2* genotype] ([Jung et al., 2008](#)). In two other studies of primarily Caucasians ([van der Logt et al., 2006](#); [Curtin et al., 2007](#)) and a study on Japanese subjects ([Yin et al., 2007](#)) no significant associations between *ADH1C* polymorphism and cancer of the colorectum were found.

Table 2.75 Studies of *ALDH2*, *ADH1B* and *ADH1C* genotype-associated risk for cancers of the head and neck

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments
Coutelle et al. (1997) , Bordeaux, France, study period NR	Oropharynx, larynx	<i>ADH1C</i>	1.0	Study participants were classified as alcoholics and consumed > 100 g ethanol per d for > 10 yr; 21 with oropharyngeal cancer, 18 with laryngeal cancer, and 37 controls with no cancer. ORs adjusted for age. Risk for laryngeal cancer in alcoholics who were <i>GSTμ</i> ⁻ and <i>ADH3*1/*1</i> was 12.9 (95% 1.8–92), compared with those who were <i>GSTμ</i> ⁻ and <i>ADH3*1/*2</i> or <i>*2/*2</i>
	Both cancer sites	<i>*1/*2</i> , <i>*2/*2</i> <i>*1/*1</i>	3.6 (0.7–10.0)	
	Oropharynx	<i>*1/*2</i> , <i>*2/*2</i> <i>*1/*1</i>	1	
	Larynx	<i>*1/*2</i> , <i>*2/*2</i> <i>*1/*1</i>	2.6 (0.7–10.0)	
			6.1 (1.3–28.6)	
Harty et al. (1997) , Puerto Rico, 1992–95	Oral cavity and pharynx	<i>ADH1C</i>	Alcohol intake	Patients (<i>n</i> = 137) with histologically confirmed oral cancer, and 146 controls
		<i>*1/*1</i>	Non-drinkers	ORs adjusted for sex, age, cigarette use, other tobacco use, fruit and vegetable intake
		<i>*1/*2</i>	1.0	
		<i>*2/*2</i>	0.9 (0.2–3.7)	
			–	
		<i>*1/*1</i>	0–14 drinks/wk	
		<i>*1/*2</i>	1.2 (0.3–5.2)	
		<i>*1/*2</i>	0.9 (0.2–4.2)	
		<i>*2/*2</i>	1.0 (0.1–12.2)	
		<i>*1/*1</i>	15–56 drinks/wk	
		<i>*1/*2</i>	3.5 (0.8–15.8)	
<i>*2/*2</i>	4.1 (0.9–18.7)			
	6.3 (1.1–36.8)			
	≥ 57 drinks/wk			
	40.1 (5.4–296.0)			
	7.0 (1.4–35.0)			
	4.4 (0.6–33.3)			
Yokoyama et al. (1998) , Japan, 1987–97	Oropharynx-larynx		11.1 (5.1–24.4)	Adjusted for age, drinking, smoking. Because the differences in odds ratio between the incident cases and the prevalent cases were small, the cases were combined.
Katoh et al. (1999) , Japan, 1992–98	Overall			Alcoholic beverage drinking not significantly associated with the risk for oral cancer. Adjusted for age, sex, smoking.
	Oral squamous-cell carcinoma	<i>ALDH2</i>	1.2 (0.7–2.1)	

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments
Bouchardy <i>et al.</i> (2000) , France, 1988–92	UADT squamous-cell carcinoma	<i>ADH1C</i>	1.0	Hospital-based case–control study. Patients with oral cavity or pharyngeal cancer (<i>n</i> = 121), laryngeal cancer (<i>n</i> = 129), and 172 controls. Patients had histologically confirmed primary SCC. All were regular smokers. Adjusted for age, sex, alcohol drinking and smoking.
		*2/*2	1.1 (0.6–2.2)	
	All oral cavity and pharynx	*1/*1	0.7 (0.4–1.4)	
	Oral cavity	*2/*2	1.0	
		*1/*2	0.9 (0.4–2.0)	
		*1/*1	0.8 (0.4–1.8)	
	Pharynx	*2/*2	1.0	
		*1/*2	1.7 (0.7–4.3)	
		*1/*1	0.8 (0.3–2.1)	
	Larynx	*2/*2	1.0	
	*1/*2	0.7 (0.4–1.4)		
	*1/*1	1.0 (0.5–1.8)		
Nomura <i>et al.</i> (2000)	Oral squamous cell carcinoma	<i>ALDH2</i>	2.9 (1.1–7.8)	Hospital-based case–control study. Habitual drinking increased the risk for oral cancer (odds ratio [95%CI], 3.9 [2.4–6.3])
		Habitual drinkers		
Olschan <i>et al.</i> (2001) , North Carolina, USA, 1994–96	UADT squamous cell carcinoma	<i>ADH1C</i>	Alcohol intake	Patients (<i>n</i> = 182), and 202 controls. Patients had pathologically confirmed SCC of oral cavity, pharynx, larynx. Adjusted for tobacco use, age, sex and race
		*1/*1 + *1/*2	Non-drinkers	
	*2/*2	1.1 (0.3–4.8)		
		1.0		
		1–19 drinks/wk		
		1.4 (0.3–5.8)		
		1.5 (0.3–8.6)		
		20–59 drinks/wk		
		2.8 (0.6–12.5)		
		2.4 (0.2–29.2)		
	≥ 60 drinks/wk			
	*1/*1 + *1/*2	5.2 (0.9–27.7)		
	*2/*2	– (no controls)		

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments
Schwartz <i>et al.</i> (2001), Washington, USA, 1985–89	Oral squamous cell carcinoma	<i>ADH1C</i>	Alcohol intake	Population-based case-control study. Oral SCC cases (<i>n</i> = 333) and 541 controls
		*1/*1	< 1 drinks/wk	Distribution of <i>ADH1C</i> among cases and controls:
		*1/*2	2.1 (0.8–5.9)	<i>ADH1C</i> *1/*1: 32.7% vs 36.5%
		*2/*2	1.7 (0.6–4.7)	<i>ADH1C</i> *1/*2: 49.0% vs 43.1%
			1.0	<i>ADH1C</i> *2/*2: 18.3% vs 20.3%
			1–14 drinks/wk	ORs adjusted for age, race and cigarette smoking
		*1/*1	2.0 (0.8–5.3)	
		*1/*2	2.1 (0.8–5.3)	
		*2/*2	1.4 (0.5–4.1)	
			15–28 drinks/wk	
		*1/*1	3.4 (1.1–10.8)	
		*1/*2	3.9 (1.3–11.8)	
		*2/*2	3.4 (1.0–11.5)	
	≥ 29 drinks/wk			
*1/*1	6.1 (1.9–19.5)			
*1/*2	8.7 (2.9–26.1)			
*2/*2	10.0 (2.5–40.2)			
	Overall			
*1/*1	1.3 (0.8–2.0)			
*1/*2	1.3 (0.9–2.0)			
*2/*2	1.0			

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments
Sturgis et al. (2001) , Houston, TX, USA, 1995–2000	Oral cavity, pharynx	<i>ADH1C</i>	Never drinkers	Cases (<i>n</i> = 229), histologically confirmed SCC of the oral cavity and pharynx, matched by age, sex and smoking status with 575 controls. ORs controlled for age, sex, and smoking status.
		*1/*1	1.0	
		*1/*2	1.5 (0.7–3.1)	
		*2/*2	1.2 (0.5–3.0)	
			Former drinkers	
		*1/*1	2.9 (1.3–6.3)	
		*1/*2	2.1 (1.0–4.4)	
		*2/*2	3.4 (1.3–8.6)	
			Current drinkers	
		*1/*1	2.6 (1.2–5.5)	
		*1/*2	2.4 (1.2–4.9)	
*2/*2	3.6 (1.6–8.1)			
	Total			
	1.0			
	1.0 (0.7–1.4)			
	1.2 (0.8–1.9)			

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments	
Yokoyama et al. (2001) , Kanagawa, Japan, 1993–2000	Oropharyngo-laryngeal squamous-cell carcinoma	ALDH2 *1/*1	1.00	Adjusted for age, drinking, smoking, <i>ALDH2</i> and <i>ADH1B</i> genotypes	
		*1/*2	18.52 (7.72–44.44)		
	Oral cavity/oropharyngeal squamous-cell carcinoma	ADH1B *1/*2 + *2/*2	1.00		
		*1/*1	6.68 (2.81–15.90)		
	Oral cavity/oropharyngeal squamous-cell carcinoma	ALDH2 *1/*1	1.00		
		*1/*2	20.83 (6.62–65.49)		
	Epilaryngeal/hypolaryngeal squamous-cell carcinoma	ADH1B *1/*2 + *2/*2	1.00		
		*1/*1	5.48 (1.77–16.96)		
	Epilaryngeal/hypolaryngeal squamous-cell carcinoma	ALDH2 *1/*1	1.00		
		*1/*2	20.83 (6.62–65.49)		
Yokoyama et al. (2002a) , Tokyo, Chiba, Japan, 1998–99	Multiple primary cancer with oesophageal squamous-cell carcinoma	ADH1B *1/*2 + *2/*2	1.00	107 patients. Multiple cancers included both multiorgan cancer and multiple intra-oesophageal squamous-cell carcinoma. Adjusted for age, sex, drinking, smoking.	
		*1/*1	5.48 (1.77–16.96)		
	Multiorgan primary cancer with head and neck squamous-cell carcinoma	ALDH2 *2/*2 or *1/*2 vs *1/*1	5.3 (1.1–51.1)		
		ALDH2 *2/*2 or *1/*2 vs *1/*1	7.4 (1.3–80.1)		
	Oesophageal SCC	ALDH2 *1/*1	1.0		Desophageal cancer, <i>n</i> = 48; oropharyngolaryngeal cancer, <i>n</i> = 29; combination, <i>n</i> = 30
		*1/*2	5.26 (1.08–51.1)		
	Oropharyngolaryngeal SCC (alone or in combination)	*2/*2	7.36 (1.29–80.7)		ORs for multiple cancer, adjusted for age, drinking, smoking

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments
Zavras et al. (2002) , Athens, Greece, 1995–98	Oral cavity	<i>ADH1C</i>	Alcohol intake Non-drinker 1.0 0.7 (0.3–2.0) 0.4 (0.1–1.8) 1–28 drinks/wk 1.7 (0.6–4.6) 1.0 (0.3–3.0) 3.4 (0.7–17.0) > 28–42 drinks/ wk 1.9 (0.3–11.6) 2.2 (0.4–12.3) – (no subjects) > 42 drinks/wk 3.0 (0.6–15.8) 11.2 (1.1–112.1) – (no subjects)	93 cases and 99 controls. Adjusted for sex, smoking and referring hospital.
		*1/*1		
		*1/*2		
		*2/*2		
		*1/*1		
		*1/*2		
		*2/*2		
		*1/*1		
		*1/*2		
		*2/*2		

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments
Risch <i>et al.</i> (2003) , Heidelberg, Germany, 1998–2000	Larynx	ADH1C *1/*2 + *2/*2 *1/*1 *1/*2 + *2/*2 *1/*1 *1/*2 + *2/*2 *1/*1 ADH1B *1/*1 *1/*2	Low intake 1.00 1.14 (0.5–2.6) Medium intake 0.85 (0.4–2.0) 1.21 (0.6–2.5) High intake 1.46 (0.7–3.1) 1.14 (0.6–2.3) Low intake 1.00 0.63 (0.2–2.8) Medium intake 0.94 (0.5–1.7) 1.85 (0.2–14.3) High intake 1.16 (0.7–2.0) 0.89 (0.3–2.5)	Cases ($n = 257$) of histologically confirmed SCC of the larynx and 251 age- and sex-matched controls. Adjusted for tobacco use. Alcohol intake (gram/d): low, 0–16.95; medium, > 16.95–50.16; high, > 50.16.
Nishimoto <i>et al.</i> (2004) , Sao Paulo, Brazil, 1995–2001	UADT (oral cavity, oropharynx, hypopharynx and larynx) cancers	ADH1C *1/*1 + *1/*2 *2/*2 *1/*1 + *1/*2 *2/*2	Lifetime alcohol intake < 100 kg 1.0 3.8 (1.5–9.7) ≤ 100 kg 1.0 0.5 (0.2–1.2)	Adjusted for age, sex and cancer in first-degree relative
Muto <i>et al.</i> (2005) , Kashiwa, Japan, 1999–2001	Squamous-cell carcinoma, oesophagus and head and neck (multiple cancers only)	ALDH2 *1 allele *2 allele ADH1C *1 allele *2 allele	1.0 5.45 (2.37 – 12.56) 1.0 2.08 (0.86–4.99)	Male and female patients, development of multiple carcinomas, adjusted for age and sex

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments
Wang et al. (2005) , Iowa, USA, 1994–97 and 2000–02	UADT (oral cavity, oropharynx, hypopharynx and larynx) squamous cell carcinoma	ADHIC*1/*2 Never drinker 1–21 drinks/wk ≥ 22 drinks/wk Total ADHIC*1/*1 Never drinker 1–21 drinks/wk ≥ 22 drinks/wk Total	0.95 (0.4–2.0) 0.5 (0.2–1.1) 0.9 (0.4–2.1) 0.8 (0.5–1.2) 0.8 (0.4–1.8) 0.6 (0.3–1.2) 0.8 (0.3–1.9) 0.7 (0.4–1.1)	Adjusted for age and tobacco pack-yr. “Total” were additionally adjusted for alcohol drinking. Reference group for each drinking level, *2/*2
Peters et al. (2005) , USA, 1999–2003	UADT (oral cavity, oropharynx, hypopharynx and larynx) squamous cell carcinoma	ADHIC*1/*1 + *1/*2 Non drinker Light drinker Heavy drinker ADHIC*2/*2 Non drinker Light drinker Heavy drinker	1.0 0.9 (0.6–1.3) 2.3 (1.4–3.8) 0.8 (0.4–1.8) 0.9 (0.6–1.6) 7.1 (2.3–22.0)	Adjusted for age, gender, race and smoking. Cutpoint for heavy alcohol is > 30 drinks per wk. Test for heavy drinking x ADH interaction, <i>P</i> = 0.05. ADHIB and ADHIC showed linkage disequilibrium.
Hashimoto et al. (2006) , Yamaguchi, Japan, 2002–04	UADT (oral cavity, oropharynx, hypopharynx and larynx) cancer	Case versus controls ALDH2 Case drinkers ALDH2	Not significantly different Significantly increased (<i>P</i> < 0.009) in cases < 66 yr compared with cases ≥ 66 yr	More cases < 66 yr were drinkers than cases ≥ 66 yr.
Homann et al. (2006) , Germany, 1999–2003	All tumours	ADHIC*1/*1 in heavy drinkers Malignant versus benign tumour Malignant vs benign tumour	2.77 (1.89–4.07) 2.2 (1.11–4.36)	818 patients with alcohol-associated esophageal (<i>n</i> = 123), head and neck (<i>n</i> = 84) and hepatocellular cancer (<i>n</i> = 86) as well as in patients with alcoholic pancreatitis (<i>n</i> = 117), alcoholic liver cirrhosis (<i>n</i> = 217), combined liver cirrhosis and pancreatitis (<i>n</i> = 17) and in alcoholics without gastrointestinal organ damage (<i>n</i> = 174). [The reference group was not reported: ADHIC*2/*2 or ADHIC*2/*2 + ADHIC*1/*1]

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments
Hashibe <i>et al.</i> (2006), Czech Republic, Poland, Romania, the Russian Federation, Slovakia, 2000–02	UADT (oral cavity, oropharynx, hypopharynx and larynx) squamous cell carcinoma	ADH1B R48H *1/*2 + *2/*2 Overall Never/light alcohol use Medium/heavy use <i>P</i> for interaction ADH1C I350V Val/Val (*1/*1) Overall Never/light alcohol use Medium/heavy use <i>P</i> for interaction ADH1C R272Q Gln/Gln (*1/*1) Overall Never/light alcohol use Medium/heavy use <i>P</i> for interaction ALDH2 +82A > G G/G Overall Never/light alcohol use Medium/heavy use <i>P</i> for interaction ALDH2 +348C > T C/C Overall Never/light alcohol use Medium/heavy use <i>P</i> for interaction	0.47 (0.32–0.70) 0.57 (0.36–0.91) 0.36 (0.17–0.77) 0.33 1.38 (1.01–1.88) 1.48 (1.02–2.15) 1.48 (0.80–2.73) 0.52 1.49 (1.08–2.05) 1.69 (1.15–2.46) 1.42 (0.76–2.66) 0.30 1.63 (0.94–2.82) 1.70 (0.88–3.29) 4.38 (1.32–14.5) 0.02 1.63 (0.92–2.89) 1.28 (0.65–2.55) 5.79 (1.49–22.5) 0.009	Reference groups were as following: ADH1B R48H, *1/*1; ADH1C I350V, Ile/Ile; ADH1C R272Q, Arg/Arg; ALDH2 +82A > G, A/A; ALDH2 +348C > T, T/T; ALDH2 –261C > T, T/T. Frequency of alcohol use was as following: Never/light drinkers, ≤ 2 times/wk; Medium/heavy ≥ 3 times/wk. Adjusted for age, sex, country, and pack-yr of tobacco smoking. Overall results were additionally adjusted for yr of alcohol drinking. Results for oral, pharyngeal, laryngeal and oesophageal cancers were also presented in the article. When results were analysed by subsite, strong main effects for ALDH2 variants were observed for squamous cell carcinoma of the oesophagus; among other subsites, only the association between ALDH2 +82A > G (A/G versus A/A) and pharyngeal cancer remained statistically significant.

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments
Hashibe et al. (2006) Contd.		ALDH2 -261C > T		
		C/C		
		Overall	1.66 (0.93–2.95)	
		Never/light alcohol use	1.29 (0.65–2.58)	
		Medium/heavy use	5.79 (1.49–22.5)	
		P for interaction	0.007	
Asakage et al. (2007) , Tokyo, Chiba, Kanagawa, Osaka, Japan 2000–03	Oral and hypo- and oropharynx	ALDH2	Alcohol intake	Patients with oropharyngeal or oral/oropharynx cancer (<i>n</i> = 53) and with hypopharyngeal cancer (<i>n</i> = 43) and 642 cancer-free men. Moderate-to-heavy drinkers: 22 g/drink, ≥ 9 drinks/wk. Adjusted for age, strong alcoholic beverage use, smoking, green-yellow vegetable use, and subcategory of alcohol drinking. When the linkage disequilibrium between <i>ADH1B</i> and <i>ADH1C</i> was taken into consideration, no relationship was found between <i>ADH1C</i> genotype and cancer risk
		*1/1	Never or light	
		*1/2	1	
			0.56 (0.20–1.59)	
		*1/1	Moderate-heavy	
			2.29 (0.94–5.57)	
		*1/2	8.26 (3.30–20.68)	
		ADH1B	Never or light	
		*1/*2 + *2/*2	1	
		*1/*1	1.00 (0.10–10.22)	
			Moderate-heavy	
		*1/*2 + *2/*2	4.75 (2.44–9.23)	
		*1/*1	26.40 (9.57–72.84)	
ADH1C	Never or light			
*1/*1	1			
*1/*2 + *2/*2	2.34 (0.58–9.48)			
	Moderate-heavy			
*1/*1	5.64 (2.82–11.31)			
*1/*2 + *2/*2	17.93 (6.43–50.00)			

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments
Hiraki <i>et al.</i> (2007), Aichi, Japan, 2001–04	Squamous cell carcinoma of the lip and oral cavity, pharynx, larynx	ADH1B His/His	1.0	Adjusted for age, sex and smoking. No cases of heavy drinkers in <i>ALDH2 Lys/Lys</i> carriers. <i>P</i> trend for heavy drinkers for <i>ADH1B</i> , 0.002 <i>P</i> trend for heavy drinkers for <i>ALDH2</i> , 0.003
		Never drinker	1.08 (0.66–1.77)	
		Moderate drinker	1.98 (1.20–3.30)	
		Heavy drinker	0.005	
		<i>P</i> for trend		
		ADH1B His/Arg	1.22 (0.63–2.35)	
		Never drinker	1.06 (0.58–1.94)	
		Moderate drinker	1.66 (1.51–4.71)	
		Heavy drinker	0.056	
		<i>P</i> for trend drinker		
		ADH2 Arg/Arg	0.50 (0.06–4.11)	
		Never drinker	2.46 (0.89–6.73)	
		Moderate drinker	9.52 (3.89–23.3)	
		Heavy drinker	0.008	
		<i>P</i> for trend		
ALDH2 Glu/Glu	1.0			
Never drinker	0.66 (0.32–1.36)			
Moderate drinker	1.41 (0.69–2.89)			
Heavy drinker	0.058			
<i>P</i> for trend				
ALDH2 Glu/Lys	0.75 (0.37–1.53)			
Never drinker	1.05 (0.50–2.20)			
Moderate drinker	3.13 (1.46–6.72)			
Heavy drinker	< 0.001			
<i>P</i> for trend				
ALDH2 Lys/Lys	0.56 (0.22–1.43)			
Never drinker	3.14 (0.45–21.6)			
Moderate drinker	n/a			
Heavy drinker	0.44			
<i>P</i> for trend				

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments
Visapää et al. (2004) , Mannheim and Heidelberg, Germany, study period NR	UADT	ADH1C *2/*2 *1/*1	1.00 1.69 (1.12–2.56)	Hospital-based case-control study. Cases ($n = 107$) of UADT cancer (99 smokers) and 103 control patients (95 smokers) with liver cirrhosis ($n = 39$), alcoholic pancreatitis ($n = 38$) or without organ injury ($n = 26$), whose alcohol intake was similar to that of the UADT patients. Adjusted for alcohol use, smoking, age, sex
Hashibe et al. (2008) , Multicenter study (see Comments), 2000–05	Oral/pharynx Larynx Oral, pharynx, larynx, and oesophagus	ADH1B *1/*1 *1/*2+*2/*2 *1/*1 *1/*2+*2/*2 *1/*1 *1/*2+*2/*2	1.00 0.45 (0.35–0.57) 1.00 0.71 (0.57–0.88) 1.00 0.56 (0.47–0.66)	Pooled analysis of studies conducted in the Russian Federation (Moscow), Poland (Lodz), Romania (Bucharest), Czech Republic (Prague, Olomouc), Slovakia (Banska Bystrica), France (Paris), Greece (Athens), Italy (Aviano, Padova, Torino), Norway (Oslo), United Kingdom (Edinburgh, Manchester, Newcastle), Spain (Barcelona), Croatia (Zagreb), Cuba, Argentina (Buenos Aires) and Brazil (Goianna, Pelotas, Rio de Janeiro, Sao Paulo). Mostly Caucasian populations, men and women, adjusted for age, gender, centre, alcohol and tobacco use. The OR (95% CI) for codominant model was 0.59 (0.50–0.69) for all four cancer sites combined.
Solomon et al. (2008) , Tamil Nadu, India, study period NR	Oral/pharynx Larynx Oral, pharynx, larynx, and oesophagus Squamous-cell carcinoma, oral cavity	ADH7 *1/*1 *1/*2+*2/*2 *1/*1 *1/*2+*2/*2 *1/*1 *1/*2+*2/*2 ADH1B *2/*1 + *2/*2 *1/*1	1.00 0.70 (0.59–0.84) 1.00 0.78 (0.59–0.93) 1.00 0.68 (0.60–0.78) Heavy drinkers 1.00 1.62 (1.08–2.14)	
Arndt et al. (2008) , Poznan, Poland, 2006–08	Laryngeal cancer	ADH1C *2/*2 *1/*2 *1/*1	1 2.65 (1.78–3.53) 1.00 1.40 (0.68–2.85) 1.53 (0.67–3.46)	No adjustment was reported

Table 2.75 (continued)

Reference, study location, period	Cancer and site	Genes involved	Relative risk (95% CI) ¹	Comments
Yokoyama et al. (2008) , Japan	Development to multiple carcinomas in oropharyngolarynx	<i>ALDH2</i> *1/*1 *1/*2 <i>ADH1B2</i> *1/*2 + *2/*2 *1/*1	1.0 4.3 (1.4–12.9) 1.0 0.8 (0.3–2.0)	Prospective part of study
Meta-analysis				
Boccia et al. (2009)	Head and neck cancer	<i>ALDH2</i> *1/*1 <i>ALDH2</i> *1/*2 <i>ALDH2</i> *2/*2	1.0 1.83 (1.21–2.77) 0.53 (0.28–1.00)	Meta-analysis of six Japanese studies. [Reduced risk with *2/*2 likely due to markedly lower levels of alcohol consumption in *2/*2 versus *1/*1 homozygotes.]

ALDH2 *1 is more active, *ADH1B* *1 is less active, and *ADH1C* *1 is more active alleles than the other allele in the respective genes.
ALDH, aldehyde dehydrogenase; *ADH*, alcohol dehydrogenase; CI, confidence interval; mo, month or months; NR, not reported; SCC, squamous cell carcinoma; vs, versus; wk, week or weeks

(d) Hepatocellular cancer

Two European studies investigated associations between *ADH1C* genotype and hepatocellular carcinoma. [Covolo et al. \(2005\)](#) reported negative results and [Homann et al. \(2006\)](#) found a positive association between *ADH1C**1/*1 and the risk for alcohol-associated hepatocellular carcinoma (Table 2.76 on-line).

(e) Cancer of the lung

No significant effect of the *ADH1C* polymorphism on the risk for cancer of the lung was found in one Japanese study ([Minegishi et al., 2007](#)) and one study in the USA ([Freudenheim et al., 2003](#)) (Table 2.76 on-line).

(f) Cancer of the female breast

Six studies conducted in Germany and the USA investigated the relationship between *ADH1C* genotype and the risk for cancer of the female breast. Three of them showed an increased risk in *ADH1C**1/*1 versus *ADH1C**1/*2 and *ADH1C**2/*2 carriers ([Freudenheim et al., 1999](#); [Coutelle et al., 2004](#); [Terry et al., 2006](#); Table 2.76 on-line). In two studies the association was more pronounced among premenopausal women ([Freudenheim et al., 1999](#); [Terry et al., 2006](#)). No significant associations between *ADH1C* polymorphism and the risk for cancer of the female breast were observed in the three other studies ([Hines et al., 2000](#); [Terry et al., 2007b](#); [Visvanathan et al., 2007](#)) as well as in one large pooled study ([Breast Cancer Association Consortium, 2006](#)).

(g) Cancer of the urinary bladder

An increased risk for cancer of the urinary bladder cancer in moderate drinkers of the *ADH1C**1/*1 genotype was reported from a Dutch study ([van Dijk et al., 2001](#)) (Table 2.76 on-line).

2.18.3 Other ADHs

In a pooled study a rare allele of *ADH7* was found to be significantly protective against UADT cancer ([Hashibe et al., 2008](#)). The role of this allele in the functional activity of the enzyme is not yet known.

2.18.4 CYP2E1

CYP2E1 is induced by chronic alcoholic beverage consumption and in addition to ethanol oxidation it plays a role in the metabolic activation of many carcinogens, including *N*-nitrosamines, benzene and aniline. The *CYP2E1* gene contains several single nucleotide polymorphisms, including C1053T (*CYP2E1**5; also referred to as *RsaI* polymorphism), G1293A (*CYP2E1**5; also referred to as *PstI* polymorphism), T7632TA (*CYP2E1**6; also referred to as *DraI* polymorphism) and G71T (*CYP2E1**7).

(a) Cancer of the oesophagus

A *CYP2E1**5B (earlier denoted *c2; *1A is the wild-type allele, earlier denoted *c1) allele-associated risk of oesophageal cancer has been reported from one study of East-Asians ([Tsutsumi et al., 1993](#)). Opposite results, with the *5B allele decreasing the risk for oesophageal cancer, have been observed in four studies of East-Asians ([Tan et al., 2000](#); [Lu et al., 2005](#); [Guo et al., 2008](#); [Qin et al., 2008](#)). The absence of significant results were reported from seven studies of East-Asians ([Morita et al., 1997](#); [Hori et al., 1997](#); [Tanabe et al., 1999](#); [Chao et al., 2000](#); [Gao et al., 2002](#); [Yang et al., 2005](#); [Wang et al., 2006b](#)), and studies of Europeans ([Lucas et al., 1996](#)), South Africans ([Li et al., 2005](#)) and Brazilians ([Rossini et al., 2007](#)) (Table 2.77 available at <http://monographs.iarc.fr/ENG/Monographs/vol100E/100E-06-Table2.77.pdf>).

(b) *Other upper aerodigestive tract cancers combined*

In seven studies from East-Asia, India, Brazil and Europe an increased risk for other upper aerodigestive tract cancer cancers in carriers of the *CYP2E1**5B allele was found ([Hildesheim et al., 1997](#); [Hung et al., 1997](#); [Bouchardy et al., 2000](#); [Gattás et al., 2006](#); [Sugimura et al., 2006](#); [Olivieri et al., 2009](#); [Ruwali et al., 2009](#)). In contrast, an inverse association between the *5B allele and oral cancer has been reported in the USA ([Liu et al., 2001](#)). No significant associations were reported from eight European studies ([Jahnke et al., 1996](#); [Lucas et al., 1996](#); [González et al., 1998](#); [Matthias et al., 1998](#); [Zavras et al., 2002](#); [Boccia et al., 2008](#)), three Japanese studies ([Katoh et al., 1999](#); [Morita et al., 1999](#); [Tanabe et al., 1999](#)), and two studies from USA ([Buch et al., 2008](#)) and India ([Soya et al., 2008](#)).

(c) *Cancers of the stomach and colorectum*

In three studies, two of Chinese ([Cai et al., 2001](#); [Wu et al., 2002](#)) and one of Caucasians ([Boccia et al., 2007](#)), increased risk for cancer of the stomach by polymorphic alleles of *CYP2E1* was found. Opposite results with the *5B allele decreasing risk of cancer of the stomach were reported from one study from Brazil ([Nishimoto et al., 2000](#)). Lack of significant associations between the *5B allele and risk of cancer of the stomach has been reported from four studies of East-Asian populations ([Kato et al., 1995, 1997](#); [Gao et al., 2002](#); [Nan et al., 2005](#)).

With regard to cancer of the colorectum, in two studies, one of Hungarians ([Kiss et al., 2000](#)) and one study of Chinese ([Gao et al., 2007](#)), an increased risk for cancer of the colorectum was demonstrated in carriers of the *CYP2E1**5B allele. From one study in Hawaii, USA ([Le Marchand et al., 2002](#)), and one study in Japan ([Morita et al., 2009](#)) an increased risk of cancer of the colorectum with 5' 96-bp insertion variant in *CYP2E1* was reported. In three other studies,

one from China ([Fan et al., 2007](#)) and two from Europe ([Landi et al., 2005](#); [van der Logt et al., 2006](#)), significant associations between *CYP2E1* polymorphism and cancer of the colorectum were not reported. In one study in Japan a decreased risk for rectal cancer in carriers of the *5B allele was found ([Morita et al., 2009](#)).

(d) *Hepatocellular cancer*

A *5B allele-associated increased risk for hepatocellular carcinoma was reported from three studies of Japanese and European populations ([Ladero et al., 1996](#); [Koide et al., 2000](#); [Munaka et al., 2003](#)). No significant association was observed in four other East Asian populations ([Lee et al., 1997](#); [Wong et al., 2000](#); [Yu et al., 2002](#); [Kato et al., 2003](#)). A decreased risk with *5B allele was reported from a Taiwan, China study ([Yu et al., 1995](#)).

(e) *Cancer of the lung*

An increased risk for cancer of the lung associated with the *CYP2E1**5B allele was found in one Japanese study ([Oyama et al., 1997](#)) and one study of mainly Caucasians ([el-Zein et al., 1997c](#)). A similar association was reported in another Japanese study ([Minegishi et al., 2007](#)), but the genotype distribution was not in Hardy-Weinberg equilibrium in the control population [so the finding of an association with cancer of the lung is most likely a false-positive result]. Opposite results with the *5B allele decreasing risk for cancer of the lung have been obtained in studies from Sweden, USA and Republic of Korea ([Persson, et al., 1993](#); [Wu et al., 1997](#); [Le Marchand et al., 1998](#); [Eom et al., 2009](#)). In eight studies, two of East Asians ([Watanabe et al., 1995](#); [Persson et al., 1999](#)), four of mixed South and North American populations ([Kato et al., 1994](#); [Hamada et al., 1995](#); [London et al., 1996](#); [Quiñones et al., 2001](#)), and one of Finns ([Hirvonen et al., 1993](#)), no significant associations were observed.

(f) Cancer of the breast

In one Korean study a non-significant increased risk for cancer of the breast associated with the *5B/*5B genotype was found ([Choi et al., 2003](#)), while in a study from Taiwan, China, an inverse association between the *5B/*5B genotype and breast cancer risk was found ([Wu et al., 2006](#)).

(g) Other cancers

For cancer of the urinary bladder no significant associations to the *5B allele were observed in an Egyptian ([Anwar et al., 1996](#)) and a German population ([Brockmüller et al., 1996](#)). Also for cancer of the kidney (renal cell) and urothelial cancer no significant associations were found in one study from Germany ([Farker et al., 1998a](#)). Three studies on East-Asian populations demonstrated a decreased risk for cancer of the prostate associated with the *5B allele ([Murata et al., 2001](#); [Yang et al., 2006a](#); [Yang et al., 2009](#)). No association between polymorphism in *CYP2E1* and risk of cancer of the pancreas was observed in an East-Asian population ([Lee et al. 2007](#)).

2.18.5 ALDH2

The variant allele *2 that encodes an inactive subunit of *ALDH2* is prevalent among East Asians (28–45%; [Goedde et al., 1992](#)), but is rare in most other populations. Individuals with inactive *ALDH2* generally abstain from heavy alcohol drinking due to subsequent acetaldehydeaemia and alcoholic flushing responses. Most homozygotes for inactive *ALDH2**2/*2 are non-drinkers or occasional drinkers, but substantial percentages of East Asians who are habitual drinkers, including alcoholics, are heterozygous *ALDH2**1/*2.

(a) Cancer of the oesophagus

The *ALDH2**2 allele has been found to be a risk factor for oesophageal cancer in 19 East-Asian studies ([Hori et al., 1997](#); [Yokoyama et al., 1998](#),

[2001, 2002, 2006a, b](#); [Tanabe et al., 1999](#); [Chao et al., 2000](#); [Matsuo et al., 2001b](#); [Boonyaphiphat et al., 2002](#); [Itoga et al., 2002](#); [Watanabe et al., 2002](#); [Yokoyama et al., 2002](#); [Yang et al., 2005, 2007](#); [Cai et al., 2006](#); [Guo et al., 2008](#); [Lee et al., 2008b](#); [Cui et al., 2009](#); [Ding et al., 2009](#); [Tables 2.73, 2.74](#)). The magnitude of the *ALDH2*-associated risk depends on the extent of the association between oesophageal cancer and alcohol consumption. The risk was observed in light-to-moderate drinkers as well as heavy drinkers, but was higher among heavier drinkers including alcoholics than the other drinkers. The findings were also supported by a meta-analysis ([Lewis & Smith, 2005](#)). In two large case-control studies in Taiwan, China ([Lee et al., 2009](#)) and Japan ([Cui et al., 2009](#)) heterozygous *ALDH2* increased the oesophageal cancer risk more prominently in younger populations. Heterozygous *ALDH2* has been consistently reported to be a strong risk factor for multiple cancers in Japanese patients with oesophageal cancer ([Yokoyama et al., 2001, 2002](#); [Muto et al., 2005](#)).

Case-control studies in high-risk rural regions in Mainland China showed modest-positive associations ([Cai et al., 2006](#); [Yang et al., 2007](#); [Ding et al., 2009](#); [Guo et al., 2008](#)) between heterozygous *ALDH2* and oesophageal cancer risk. In these studies, the risks were more distinct where the impact of alcohol consumption on oesophageal cancer was more distinct and when only male populations were evaluated. [Tian et al. \(1998\)](#) reported no significant association between *ALDH2* polymorphism and oesophageal cancer, but this study included only cases of oesophageal squamous carcinoma and the *ALDH2* gene frequencies were compared just to other published data. In addition to the data on East-Asian populations, the association between oesophageal cancer and the *ALDH2**2 allele has been found in a study in South Africa ([Li et al., 2008a](#)). In addition, the +82A > G, +348C > T and –261C > T variants of *ALDH2* (without known functional actions) have been related to

oesophageal cancer in a large pooled European study ([Hashibe et al., 2006](#)).

(b) Other upper aerodigestive tract cancer

In 10 Japanese studies, the *ALDH2**2 allele has been shown to be a risk factor for upper aerodigestive tract cancer ([Yokoyama et al., 1998, 2001, 2002, 2006b, 2008](#); [Nomura et al., 2000](#); [Muto et al., 2005](#); [Hashimoto et al., 2006](#); [Asakage et al., 2007](#); [Hiraki et al., 2007](#); [Table 2.75](#)). In one Japanese study significant associations between the *2 allele and oral cancer were not found ([Katoh et al., 1999](#)); in this study a significant association between risk of oral cancer and consumption of alcoholic beverages was not found either. A meta-analysis of these Japanese studies showed that heterozygous *ALDH2* increased upper aerodigestive tract cancer risks more strongly in heavy drinkers including alcoholics than the other drinkers ([Boccia et al., 2009](#)). In one Japanese study a higher frequency of heterozygous *ALDH2* in younger drinkers with upper aerodigestive tract cancer was found ([Hashimoto et al., 2006](#)). Heterozygous *ALDH2* has been reported to be a strong risk factor for multiple cancers in Japanese patients with upper aerodigestive tract cancers ([Yokoyama et al., 2001, 2002, 2008](#); [Muto et al., 2005](#)). The other *ALDH2* variants (reported by [Hashibe et al., 2006](#)) did not significantly affect the risk of oral and other upper aerodigestive tract cancers (excluding oesophageal cancer).

(c) Cancers of the stomach, colorectum and pancreas

In two Japanese studies an increased risk for cancer of the stomach by the *ALDH2**2 allele has been reported ([Yokoyama et al., 1998, 2007b](#); [Table 2.76 on-line](#)). Such an association was reported from another Japanese study ([Yokoyama et al., 2001](#)) when all gastric cancer cases, including gastric cancer alone or combined with upper aerodigestive tract cancers were considered. However, when only cases of cancer of the stomach alone were included

in the analyses, there was no association with *ALDH2*. In a study of Polish consumers of alcoholic beverages an increased risk for cancer of the stomach by the *ALDH2* +82A > G alleles was found ([Zhang et al., 2007b](#)). No significant associations with the *2 allele were reported from a study from Republic of Korea ([Nan et al., 2005](#)).

Increased risks of colon and/or rectal cancer have been associated with the *2 allele in three East-Asian studies ([Yokoyama et al., 1998](#); [Murata et al., 1999](#); [Matsuo et al., 2002](#)). The *2 allele has also been associated with lower risk in one Chinese ([Gao et al., 2008](#)) and a Japanese ([Yin et al., 2007](#)) study. No significant differences were seen in four Japanese studies ([Takeshita et al., 2000a](#); [Hirose et al., 2005](#); [Otani et al., 2005](#); [Matsuo et al., 2006a](#)).

In one of two Japanese studies [Kanda et al. \(2009\)](#) reported increased risk for the *ALDH2**2 allele for cancer of the pancreas; no significant associations were found by [Miyasaka et al. \(2005\)](#).

(d) Hepatocellular cancer

In four of 11 Japanese and Chinese studies an increased risk for hepatocellular carcinoma in carriers of the *ALDH2**2 allele has been found ([Kato et al., 2003](#); [Munaka et al., 2003](#); [Sakamoto et al., 2006](#); [Ding et al., 2008](#)) ([Table 2.76 on-line](#)). Four Japanese ([Shibata et al., 1998](#); [Yokoyama et al., 1998](#); [Koide et al., 2000](#); [Takeshita et al., 2000b](#)) and one Chinese ([Yu et al., 2002](#)) study reported no significant associations between *ALDH2* polymorphism and hepatocellular cancer.

(e) Cancer of the lung

An increased risk for lung cancer associated with *ALDH2**2 alleles has been observed in three studies, two from Japan ([Yokoyama et al., 1998](#); [Minegishi et al., 2007](#)) and one from Republic of Korea ([Eom et al., 2009](#)) ([Table 2.76 on-line](#)).

(f) Cancer of the female breast

No significant association between *ALDH2* polymorphism and risk of cancer of the breast has been observed in a Korean ([Choi et al., 2003](#)) and a Spanish population ([Ribas et al., 2008](#)) (Table 2.76 on-line).

2.19 Synthesis

2.19.1 Oral cavity and pharynx

Data published since the previous *IARC monograph* ([IARC, 2010](#)) support the conclusion that consumption of alcoholic beverages is causally related to cancer of the oral cavity and pharynx. Increasing alcohol consumption increases risk in a dose-dependent manner, does not vary materially by beverage type or sex and the association is not due to chance, bias or confounding.

2.19.2 Larynx

Data published since the previous *IARC Monograph* ([IARC, 2010](#)) supports the conclusion that consumption of alcoholic beverages is causally related to cancer of the larynx. Increasing alcohol consumption increases risk in a dose-dependent manner, does not vary materially by beverage type or sex, and chance, bias and confounding can be ruled out.

2.19.3 Oesophagus

Data published since the previous *IARC Monograph* ([IARC, 2010](#)) supports the conclusion that consumption of alcoholic beverages is causally related to squamous cell carcinoma of the oesophagus. Increasing alcohol consumption increases risk in a dose-dependent manner, does not vary materially by beverage type or sex, and chance, bias and confounding can be ruled out. There is now a substantial body of evidence that alcoholic beverage consumption is not associated with adenocarcinoma of the oesophagus.

2.19.4 Upper aerodigestive tract combined

There is evidence that consumption of alcoholic beverages is causally related to cancer of the upper aerodigestive tract, as it is for cancer of the oral cavity and pharynx, larynx and oesophagus separately. Increasing alcohol consumption increases risk in a dose-dependent manner, does not vary materially by beverage type or sex and chance, bias and confounding can be ruled out.

2.19.5 Colon and rectum

Data published since the previous *IARC Monograph* ([IARC, 2010](#)) supports the conclusion that consumption of alcoholic beverages is causally related to cancer of the colorectum. Most of the evidence suggests that consumption of alcoholic beverages is positively associated with both cancer of the colon and cancer of the rectum, and is similar in men and women, although the data are not entirely consistent. Similarly, there is some evidence that risk may only be increased at relatively high levels of intake (i.e. > 30 g/d). There is consistent evidence that risk does not differ by beverage type; whether the risk associated with consumption of alcoholic beverages differs by smoking status or intake of dietary folate is inconsistent.

2.19.6 Liver

Data published since the previous *IARC Monograph* ([IARC, 2010](#)) support the previous conclusion that the consumption of alcoholic beverages is causally related to hepatocellular carcinoma. It is not possible to draw any conclusion concerning consumption of alcoholic beverages and risk of cholangiocarcinoma.

2.19.7 Stomach

Results on the association between consumption of alcoholic beverages and cancer of the stomach are difficult to interpret due to the lack

of information on important confounders, such as possible dietary deficiencies.

2.19.8 *Pancreas*

There is accumulating evidence that high alcohol intake (i.e. ≥ 30 g/d) is associated with a small increased risk for cancer of the pancreas. However, the possibility that residual confounding by smoking may partly explain this association cannot be excluded. Whether the risk associated with heavy alcohol consumption differs by beverage type, smoking status or body mass index is unclear.

2.19.9 *Lung*

Available data are inadequate to determine a causal association between the consumption of alcoholic beverages and cancer of the lung. Although adjustment for tobacco smoking was attempted in many studies, residual confounding cannot be excluded for those analyses that found a positive association with consumption of alcoholic beverages. For those studies that attempted to evaluate risk for cancer of the lung from the consumption of alcoholic beverages in non-smokers, small numbers of cases, or few subjects with high consumption of alcoholic beverages, precluded detection of an association.

2.19.10 *Breast*

Occurrence of cancer of the female breast is causally associated with the consumption of alcoholic beverages. Cancer risk increases proportionately according to the amount of alcohol consumed, with an increase in risk of up to 12% for each additional drink consumed regularly each day (equivalent to about 10 g/d). The risk does not appear to vary significantly by beverage type or smoking status. It remains unclear whether the association of alcohol beverage consumption with risk for cancer of the female breast varies

by use of hormone-replacement therapy or by tumour receptor status.

The evidence that alcoholic beverage consumption is associated with cancer of the male breast remains inconsistent.

2.19.11 *Uterine cervix*

The weak associations noted in some studies for consumption of alcoholic beverages and risk of cancer of the uterine cervix are sufficient to draw any conclusion on causality. Few studies were able to adjust for the known risk factors for the disease.

2.19.12 *Endometrium*

The evidence for an association between consumption of alcoholic beverages and risk for cancer of the endometrium is inconsistent. The majority of studies show no association; the few that show an inverse association were not able to adjust for tobacco smoking.

Among both the cohort and case-control studies, there was no consistent evidence of an interaction between consumption of alcoholic beverages and different variables known or suspected to be associated with cancer of the endometrium, such as use of hormone replacement therapy, body size, age, tobacco smoking, parity, education, physical activity, energy intake and other dietary aspects, oral contraceptive use or menopausal status.

2.19.13 *Ovary*

There is little evidence for an association between consumption of alcoholic beverages and risk for cancer of the ovary. The majority of studies show no association.

2.19.14 Prostate

There is little evidence for an association between consumption of alcoholic beverages and risk of cancer of the prostate. Although in some studies positive associations were found for advanced disease, the majority of studies show no association.

2.19.15 Kidney

There is no causal association between consumption of alcoholic beverages and cancer of the kidney.

2.19.16 Urinary bladder

Overall, the studies on cancer of the urinary bladder suggest no association with consumption of alcoholic beverages.

2.19.17 Haematopoietic malignancies

In cohort studies in the general population, most forms of lymphomas and leukaemias have shown no or inverse associations with consumption of alcoholic beverages; studies that assessed risk for non-Hodgkin lymphoma, the form of lymphomas and leukaemias most studied, generally found an inverse association.

There were consistent inverse associations in case-control studies investigating ever alcohol consumption and risk for Hodgkin lymphoma, with no significant differences between alcoholic beverage types. A large pooled study observed a lower risk of several histological subtypes, such as Burkitt, B-cell, follicular and T-cell lymphomas among ever drinkers.

No clear patterns of association between consumption of alcoholic beverages and risk of all leukaemias combined were shown in case-control studies. Two studies indicated increased risk of acute lymphocytic leukaemia with any or heavy alcohol drinking, and also increased risk of chronic lymphocytic leukaemia among wine

drinkers, but there was no consistent pattern of association for different types of leukaemias. In most studies on multiple myeloma no consistent results were observed.

2.19.18 Other cancers

It is not possible to draw any conclusions regarding the association between intake of alcoholic beverages and risk for cancers of the brain and thyroid, melanoma and non-melanoma skin cancers.

2.19.19 Parental exposure and childhood cancers

Results for the association between maternal consumption of alcohol before or during pregnancy and risk of acute lymphocytic leukaemia, acute lymphocytic leukaemia and acute leukaemia in the offspring are inconsistent.

2.19.20 Polymorphisms and genetic susceptibility

(a) *ADH1B*

The available genetic epidemiological data suggest a positive association between *ADH1B**1/*1 polymorphism and cancer of the oesophagus, and cancers of the upper aerodigestive tract combined. The relationship between *ADH1B* genotype and cancer in other organs is inconclusive because of the small number of studies.

(b) *ADH1C*

The relationship between *ADH1C* genotype and cancer at any site is inconclusive, primarily because of the small number of studies.

(c) *ALDH2*

The available genetic epidemiological data provides ample evidence for a strong contribution of heterozygous *ALDH2* genotype to the

development of alcohol-related cancer in the oesophagus and in the upper aerodigestive tract. While it is often difficult to differentiate clearly between exact locations of tumours in the oropharyngolaryngeal area based on the available published data, there is also strong evidence for a contribution of heterozygous *ALDH2* genotype to the development of alcohol-related cancer in the oropharyngolarynx as a whole, and especially in the hypopharynx. However, the epidemiological studies provide suggestive but inconclusive data for some association of heterozygous *ALDH2* genotype and alcohol-related cancers in the individual oropharyngolaryngeal subsites of the oral cavity, oropharynx and larynx.

The evidence for cancers of the stomach, colorectum, pancreas, liver, breast, bladder and prostate is inconclusive.

3. Cancer in Experimental Animals

Consumption of alcoholic beverages was evaluated in 2007 ([IARC, 2010](#)). The studies described below were considered; no new studies have been published since.

An issue in evaluating bioassays of ethanol is the nutritive value of this substance, which results in a hyperalimentation of alcohol-fed animals. For rigorous evaluation of the carcinogenicity of alcohol by ingestion in experimental animals, controls must be pair fed to equalize caloric intake.

3.1 Oral administration of ethanol in the drinking-water

Study design and results of studies of oral administration of ethanol in drinking-water are presented in [Table 3.1](#).

3.1.1 Rat

Eight groups of 50 male and 50 female Sprague-Dawley rats received either 1% or 3% ethanol or an equicaloric amount of glucose in a semisynthetic liquid diet for 120 weeks ([Holmberg & Ekström, 1995](#)). Males were given 70 mL/day and females 60 mL/day of liquid diet. No tumours developed in male rats. There was a significant ($P < 0.05$) increase in pituitary tumours [not further specified] among 3% ethyl alcohol-treated females (80%) than among high-dose glucose-treated animals (58%). There was also an increase ($P < 0.05$) in mammary gland fibromas, fibroadenomas and adenomas combined, in the 1% ethyl alcohol-treated females compared with the low-dose glucose animals [no incidence provided].

Male Sprague-Dawley rats administered 5% ethanol in the drinking-water for 130 weeks developed hepatocellular carcinomas (8/79 versus 1/80 control rats). Additionally, the authors reported an increase in the incidence of hyperplastic liver nodules in the ethanol group. Pancreatic adenomas, adrenal gland adenomas, and pituitary adenomas occurred in the ethanol group in 18% (14/79), 18% (14/79), and 33% (26/79) of the animals, respectively. No tumours of the pancreas or adrenal gland were found in control rats. Pituitary adenomas were found in 8/80 control rats ([Radike et al., 1981](#)).

In other experiments, the chronic administration of 5% or 10% ethanol had no effect on liver carcinogenesis of Wistar or F344 rats ([Shibayama et al., 1993](#); [Yamagiwa et al., 1994](#); [Wanibuchi et al., 2006](#)).

Sprague-Dawley rats and their offspring received either 10% ethanol or no ethanol in the drinking-water *ad libitum* starting at 39 weeks of age, 7 days before mating or from embryo life (offspring) until death. The intake of fluid was lower in the treated group but no difference in body weight was noted. An increased incidence of total malignant tumours was noted in female

Table 3.1 Carcinogenicity studies on ethyl alcohol administered in the drinking-water to experimental animals

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Sprague-Dawley (M) 130 wk Radlike et al. (1981)	5% 7 d/wk 79 animals 80 animals (controls)	Liver	[<i>P</i> < 0.05]	
		Carcinoma Control (1/80) 5% Ethanol (8/79)		
		Pituitary gland	[<i>P</i> < 0.001]	
		Adenoma Control (8/80) 5% Ethanol (26/79)		
		Adrenal gland	[<i>P</i> < 0.0001]	
Rat, Sprague-Dawley (M) 140 wk Soffritti et al. (2002a)	10% 7 d/wk 110 animals 110 animals (controls)	Pancreas	[<i>P</i> < 0.0001]	
		Adenoma Control (0/80) 5% Ethanol (14/79)		
		Testes	[NS]	
		Seminoma Control (0/80) 5% Ethanol (3/79)		
Rat, Sprague-Dawley (M) 140 wk Soffritti et al. (2002a)	10% 7 d/wk 110 animals 110 animals (controls)	Forestomach	[<i>P</i> < 0.01]	Animals were breeder
		Benign Control (1/110) 10% Ethanol (8/110)		
		Benign and malignant Control (1/110) 10% Ethanol (10/110)	[<i>P</i> < 0.01]	
		Osteosarcoma Control (1/110) 10% Ethanol (12/110)	[<i>P</i> = 0.0042]	
		Head and other sites	<i>P</i> < 0.01	
		Carcinoma Control (3/110) 10% Ethanol (15/110)		
		Testes	[<i>P</i> = 0.013]	
		Interstitial cell adenoma Control (9/110) 10% Ethanol (23/110)		
		Lymphomas and leukaemias Control (17/110) 10% Ethanol (46/110)	[<i>P</i> < 0.0001]	
		Oral cavity, lips and tongue	<i>P</i> < 0.05	
Rat, Sprague-Dawley (F) 140 wk Soffritti et al. (2002a)	10% 7 d/wk 110 animals 110 animals (controls)	Oral cavity, lips and tongue		
		Carcinoma Control (2/110) 10% Ethanol (12/110)		

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Sprague-Dawley (M) 179 wk Soffritti et al. (2002a)	10% 7 d/wk 30 animals 49 animals (controls)	Oral cavity, lips and tongue Carcinoma Control (2/49) 10% Ethanol (10/30)	$P < 0.01$	Animals were offsprings
Rat, Sprague-Dawley (F) 179 wk Soffritti et al. (2002a)	10% 7 d/wk 39 animals/group 55 animals (controls)	Oral cavity, lips and tongue Carcinoma Control (3/55) 10% Ethanol (16/39)	$P < 0.01$	Animals were offsprings
Mouse B6C3F1 (M) 104 wk Beland et al. (2005)	0 (control), 2.5%, 5% 7 d/wk 48 animals/group	Liver Adenoma or Carcinoma Control (12/46) 2.5% Ethanol (16/47) 5% Ethanol (25/48) Adenoma Control (7/46) 2.5% Ethanol (12/47) 5% Ethanol (19/48)	$P < 0.05$ dose-related trend, $P = 0.056$ (5% ethanol) $P < 0.05$ dose-related trend, $P < 0.05$ (5% Ethanol)	
Mouse, ICR (F) 106 wk Watabiki et al. (2000)	10–15% 7 d/wk 20 animals/group	Mammary gland Adenocarcinoma Control (0/20) 10–15% Ethanol (9/20)	$[P = 0.012]$	
Mouse, C57/ BL6APCmin (M) 10 wk Roy et al. (2002)	15% alternating with 20% every other d 12 animals/group	Intestine Adenoma Tumor multiplicity Control (26.8) 15–20% Ethanol (36.9)	$P < 0.05$	

d, day or days; F, female; M, male; NS, not significant; wk, week or weeks

breeders and male offspring. This was due to a significant increase in the incidence of head and neck carcinomas (oral cavity, lips, tongue) in male and female breeders and male and female offspring; benign and combined benign and malignant tumours of the forestomach in male breeders; and combined lymphomas and leukemias in female breeders. Increases in the incidence of interstitial-cell adenomas of the testis and osteosarcomas of the head and other sites were also observed in male breeders (Soffritti *et al.*, 2002a). [The Working Group noted that some statements reporting increased incidence were not supported by statistical analyses performed by the Working Group].

3.1.2 Mouse

B6C3F₁ male and female mice received 2.5% or 5% of ethanol in drinking-water for 104 weeks. No significant difference in tumour incidence at any site was observed in females. There was a significant dose-related trend for the incidence of hepatocellular adenomas, and hepatocellular adenomas and carcinomas combined in male mice. The administration of 5% ethanol resulted in an increase in the incidence of hepatocellular adenomas ($P < 0.05$) and a marginal increase ($P = 0.056$) in the incidence of hepatocellular adenomas and carcinomas combined in male mice (NTP, 2004; Beland *et al.*, 2005).

ICR female mice received 10% ethanol in the drinking-water for 2 months and then 15% ethanol in the drinking-water for 23 months. Mammary gland tumours (papillary or medullary adenocarcinomas) were found in 9/20 mice given ethanol in drinking-water compared with 0/20 control mice [$P = 0.012$] (Watabiki *et al.*, 2000).

C57BL/6^{APC^{min}} male mice received ethanol in drinking-water at doses between 15 and 20% daily for 10 weeks. This treatment increased intestinal adenoma multiplicity (Roy *et al.*, 2002).

3.2 Oral administration of acetaldehyde in drinking-water

See [Table 3.2](#).

Acetaldehyde was evaluated in 1984 (IARC, 1985), 1998 (IARC, 1999), and 2007 (IARC, 2010).

3.2.1 Rat

Sprague-Dawley male and female rats received acetaldehyde in the drinking-water at doses of 50, 250, 500, 1500 and 2500 mg/L for 161 weeks. With the exception of male rats treated with 1500 mg/L, the administration of acetaldehyde to male Sprague-Dawley rats resulted in a marginal dose-dependent increase in incidence of pancreatic islet cell adenomas. The incidence of pancreatic islet cell adenoma was significantly higher (18%; 9/50) in male rats exposed to the high dose of acetaldehyde (2500 mg/L) compared to 4% (2/50) in the control group. Acetaldehyde caused an increased incidence of head osteosarcomas in the 50 and 2500 mg/L groups. Additionally, ingestion of acetaldehyde resulted in a higher incidence of lymphomas and leukemias in male rats exposed to acetaldehyde at doses of 50 mg/L and 1500 mg/L. Acetaldehyde also caused an increase in lymphomas and leukemias in female rats, 16% in rats exposed to 250 mg/mL compared to 4% in control animals. A higher incidence of mammary gland adenocarcinomas and uterine adenocarcinomas was found in the groups of females exposed to 500 mg/L and 250 mg/L, respectively (Soffritti *et al.*, 2002b). [The Working Group noted that a variety of tumours were increased. However, no obvious dose-response relationship was observed.]

3.3 Co-carcinogenicity studies on alcohol administered in drinking-water

A comprehensive analysis of the studies on the co-carcinogenicity of ethanol was presented in the previous *IARC Monograph* ([IARC, 2010](#)). Simultaneous administration of alcohol with known carcinogens enhanced tumour development. A selection of positive studies is summarized below.

3.3.1 Rat

Chronic administration of ethanol potentiates the development of tumours in experimental animals induced by chemical agents.

Two groups of 80 Sprague-Dawley rats received either vinyl chloride or vinyl chloride and 5% ethanol in the drinking-water for 130 weeks. Increases in the incidence of liver carcinomas and liver angiosarcomas were observed in the vinyl chloride and ethanol group compared to the vinyl chloride treated control rats. In rats exposed to vinyl chloride and ethanol 15% developed pancreatic adenomas, whereas no tumours were found in control rats ([Radike et al., 1981](#)).

Fischer 344/DuCrj rats were fed 200 ppm 2-amino-3,8-dimethylimidazo[4,5]quinoxaline (MeIQx). After 8 weeks, rats were subdivided to receive either drinking-water or 0.1, 0.3, 1, 3, or 10% ethanol in the drinking-water. In rats administered MeIQx in the diet, the incidence of hepatocellular adenoma, carcinoma and adenoma plus carcinoma was increased by ethanol consumption in a dose-dependent manner ($P < 0.001$) ([Kushida et al., 2005](#)).

Chronic ethanol administration in drinking-water to male F344 rats for 55 weeks after treatment with the chemical carcinogens *N'*-nitrosornicotine (NNN) or 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK) increased the incidence of tumours of the oesophagus, oral cavity and

lungs. NNK also induced liver tumours, which were significantly increased by ethanol ingestion ([Nachiappan et al., 1994](#)). Similarly, administration of 5% ethanol to male Wistar rats enhanced the oesophageal tumourigenesis induced by *N*-nitrosomethylbenzylamine ([Tsutsumi et al., 2006](#)). The enhancing effect of ethanol on *N*-nitrosodiethylamine (NDEA)-induced oesophageal carcinogenesis was also observed in male Fischer 344 rats. Two groups of Fischer 344 rats received either 50 ppm NDEA dissolved in 10% ethanol or 50 ppm NDEA solution in water, respectively, for 8 weeks. Rats were maintained on tap water and basal diet for 96 weeks. The incidence of oesophageal papillomas or carcinomas in rats that received NDEA dissolved in 10% ethanol was higher than in rats that received NDEA alone ($P < 0.01$) ([Aze et al., 1993](#)).

Chronic intake of 10% ethanol for 56 weeks enhanced hepatocarcinogenesis induced by oral administration of combined ethinylestradiol and norethindrone acetate in male and especially female Wistar rats ([Yamagiwa et al., 1994](#)). Long-term ethanol treatment had a similar effect in male rats on liver preneoplastic lesions induced by aflatoxin B₁ ([Tanaka et al., 1989](#)), *N*-nitrosomorpholine ([Tatsuta et al., 1997](#)), MeIQx ([Wanibuchi et al., 2006](#)), and NDEA and 2-acetylaminofluorene ([Pires et al., 2008](#)).

The administration of ethanol (15% in the drinking-water) during the initiation and promotion stages of mammary gland carcinogenesis, induced by *N*-methylnitrosourea in female Sprague-Dawley rats, increased the number of mammary adenocarcinomas compared to control rats. Likewise, ethanol intake during the promotion stage resulted in a greater number of mammary adenocarcinomas ([Singletary et al., 1995](#)). The administration of ethyl alcohol to pregnant female Sprague-Dawley rats during gestation significantly increased mammary gland tumours induced by 7,12-dimethylbenz[*a*]anthracene (DMBA) in offspring, as evidenced

Table 3.2 Carcinogenicity studies on acetaldehyde administered with drinking-water to rats

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Sprague-Dawley (M) 161 wk Soffritti et al. (2002b)	50 mg/L 7 d/wk 50 animals/group	Head	Osteosarcoma Control (0/50) Acetaldehyde (5/50)	$P < 0.05$
	2500 mg/L 7 d/wk 50 animals/group	Head	Osteosarcoma Control (0/50) Acetaldehyde (7/50)	$P < 0.05$
	50 mg/L 7 d/wk 50 animals/group	Lymphomas and leukemias	Control (6/50) Acetaldehyde (14/50)	$[P = 0.039]$
	1500 mg/L 7 d/wk 50 animals/group	Lymphomas and leukemias	Control (6/50) Acetaldehyde (15/50)	$[P = 0.024]$
	2500 mg/L 7 d/wk 50 animals/group	Pancreas	Islet cell adenoma Control (2/50) Acetaldehyde (9/50)	$[P = 0.026]$
	Rat, Sprague-Dawley (F) 161 wk Soffritti et al. (2002b)	250 mg/L 7 d/wk 50 animals/group	Lymphomas and leukemias	Control (2/50) Acetaldehyde (8/50)
	500 mg/L 7 d/wk 50 animals/group	Mammary gland	Adenocarcinoma Control (3/50) Acetaldehyde (10/50)	$[P = 0.036]$
	250 mg/L 7 d/wk 50 animals/group	Uterus	Adenocarcinoma Control (0/50) Acetaldehyde (5/50)	$[P = 0.028]$

d, day or days; F, female; M, male; wk, week or weeks

by a greater tumour multiplicity ([Hilakivi-Clarke et al., 2004](#)).

3.3.2 Mouse

Treatment of CF-1 male mice with 6% ethanol in the drinking-water increased development of invasive pancreatic adenocarcinoma induced by DMBA ([Wendt et al., 2007](#)).

As part of the study to investigate the effect of ethanol on the carcinogenicity of NDEA, strain A male mice were administered NDEA in the drinking-water with or without 10% ethanol for 4 weeks and were maintained thereafter for 32 weeks on tap-water and basal diet. Ethanol strongly potentiated the tumorigenic effect of NDEA in the forestomach and the lung ([Anderson et al., 1993](#)).

The effect of ethanol on the carcinogenicity of nitrosamines was comprehensively summarized in the previous *IARC Monographs* ([IARC, 1988, 2010](#)).

3.4 Synthesis

Administration of ethanol in the drinking-water increased the incidence of cancers of the head and neck and the liver, benign tumours of the adrenal glands, pituitary gland, testes, and pancreas, osteosarcomas of the head and other sites, forestomach tumours, and combined lymphomas and leukemias in rats and liver tumours and mammary gland adenocarcinomas in mice.

Administration of acetaldehyde in the drinking-water increased the incidence of pancreatic adenomas, combined lymphomas and leukaemias, uterine and mammary gland adenocarcinomas, and head osteosarcomas in rats.

Co-administration of ethanol in the drinking-water with several known carcinogens enhanced tumour development in rats and mice.

4. Other Relevant Data

The current knowledge on mechanistic and other data relevant to the carcinogenicity of alcoholic beverages was reported in the recent *IARC Monograph* ([IARC, 2010](#)). A synthesis of these data is presented below.

4.1 Absorption, distribution, metabolism and excretion

The biomedical effects of alcoholic beverages either originate from the properties of the ethanol major component, or from its metabolism. The metabolism of ethanol is depicted in Fig. 4.1. Ethanol is metabolized to acetaldehyde by three major pathways: the alcohol dehydrogenase (ADH) pathway, the microsomal ethanol oxidizing cytochrome P450 (CYP) pathway, and the catalase-H₂O₂ system. Acetaldehyde, to which many deleterious effects of ethanol can be attributed, is oxidized to acetate primarily by acetaldehyde dehydrogenases (ALDHs) ([Vasiliou et al., 2004](#)). The four pharmacokinetic parameters, absorption, distribution, metabolism and excretion, that define the level of ethanol and/or its metabolites in different tissues, are relevant for consideration.

4.1.1 Ethanol

(a) Absorption and distribution

The absorption of orally ingested alcohol starts in the upper digestive mucosa and the stomach, but the bulk is absorbed by simple diffusion in the small intestine into the bloodstream. Hereafter, alcohol is distributed into the body water. The absorption, immediately followed by the distribution phase, largely determines the ascending part and the peak of the blood-alcohol curve. Food in conjunction with alcohol drinking lowers the rate of absorption and diminishes the peak alcohol concentration, while fasting and dehydration create opposite effects. The distribution process produces slightly lower ethanol levels in venous blood ([Jones et al., 2004](#)) and urine ([Jones 2006](#)) compared with arterial blood levels during the absorption phase. More fat and less body water per unit body-mass create higher blood alcohol levels, which explains why women on average reach a 10–15% higher blood-alcohol concentration compared with the same amount of alcohol per body-mass ingested by men ([Goist & Sutker, 1985](#)).

(b) Metabolism and excretion

It is generally believed that more than 90% of the ingested alcohol is oxidized in the liver. The remaining extrahepatic alcohol oxidation and other modes of elimination take place in the gastrointestinal mucosa and bacteria, via oral bacteria, the kidneys and other peripheral tissues, by excretion of body fluids (urine and sweat) and via exhalation. First-pass metabolism, i.e. when the ethanol is oxidized at its first passage through the oral cavity, gut and liver, reduces the amount of ethanol that reaches target organs. The relative contribution of first-pass metabolism to alcohol oxidation is debatable ([Lim et al., 1993](#); [Levitt & Levitt, 2000](#)). However, the smaller the alcohol amount and the slower the alcohol absorption, the greater the relative contribution of first-pass

oxidation in overall alcohol elimination ([Levitt & Levitt, 1998](#)).

(i) *Endogenous alcohol formation*

In addition to ingestion via consumption of alcoholic beverages, small amounts of ethanol are also produced endogenously in normal intermediary metabolism ([Ostrovsky, 1986](#)) and by microbial formation, especially in the gastrointestinal tract ([Krebs & Perkins, 1970](#)). The resulting concentrations in human venous blood are estimated to vary between 0–50 μM ([Jones et al., 1983](#); [Watanabe-Suzuki et al., 1999](#)). Based on case reports ([Kaji et al., 1984](#); [Spinucci et al., 2006](#)) and on data from experimental animals ([Krebs & Perkins, 1970](#)), it has been shown that considerably higher concentrations exist in the gastrointestinal tract. The relevance of endogenous metabolism is further discussed in Section 4.3.1.

(ii) *Alcohol dehydrogenase pathway*

The oxidation of ethanol is largely catalysed by cytosolic ADHs, primarily by the low- K_m variants in the liver. Because of the low K_m (0.05–4.2 mM) ADH quickly becomes saturated and the reaction follows zero-order kinetics with a constant rate for ethanol oxidation. In addition to the enzyme activity, the ADH-mediated ethanol oxidation rate is strictly regulated by the mitochondrial reoxidation of the reduced co-enzyme nicotinamide adenine dinucleotide (NADH) to the oxidized form, nicotinamide adenine nucleotide (NAD⁺) ([Zakhari, 2006](#)). This explains why, in spite of huge variations in ADH activity, relatively small effects on the overall alcohol oxidation rate have been observed. The impact of the hepatic redox state is even more apparent under fasting conditions, which are well known to slow down the rate of alcohol oxidation ([Rogers et al., 1987](#)), most likely due to limitations in the mitochondrial reoxidation of NADH ([Lisander et al., 2006](#)). The less alcohol is ingested the larger the

contribution of ADH activity in the regulation of the rate of alcohol oxidation (see Fig. 4.1).

Human ADHs

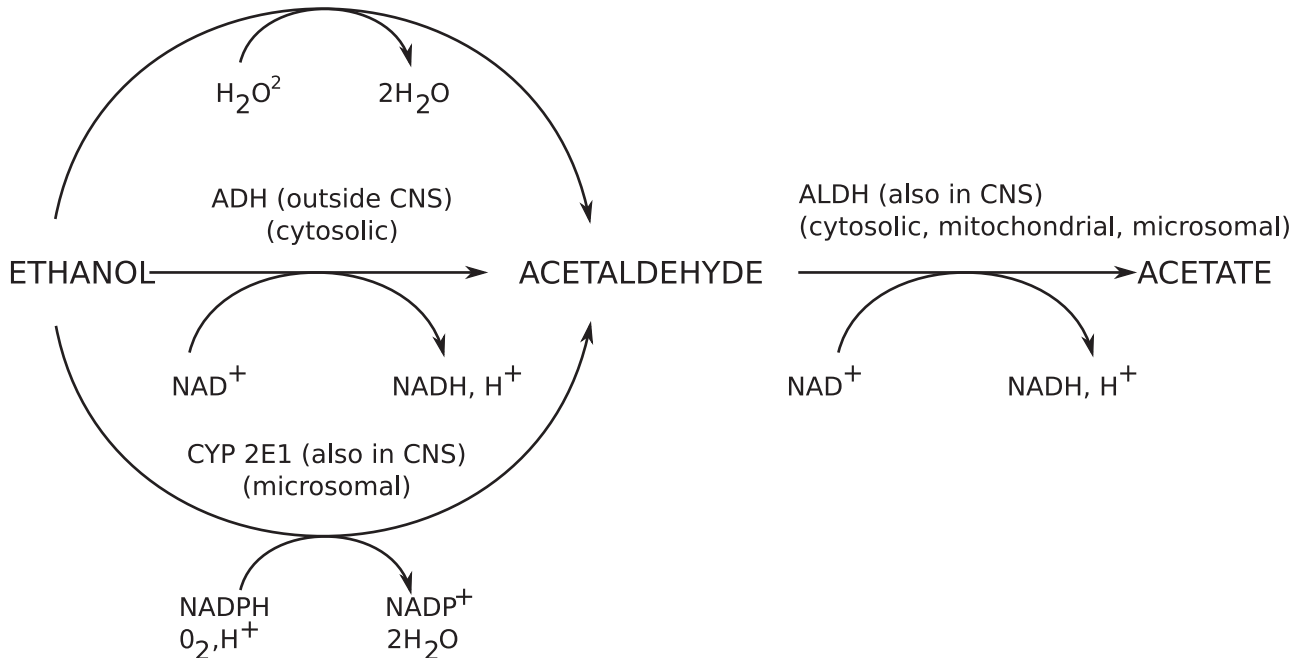
Three different nomenclature systems have been proposed for the human ADH genes ([Table 4.1](#)). The official nomenclature approved by the Human Genome Organization (HUGO) (www.gene.ucl.ac.uk/nomenclature) will be used here throughout.

Seven human ADHs have been isolated that are divided into five classes on the basis on similarities in their amino acid sequences and kinetic properties ([Table 4.1](#)). They are dimeric enzymes consisting of two 40kDa subunits named α , β , γ , π , χ and either σ or μ . Class I comprises three enzymes: ADH1A, which contains at least one α subunit ($\alpha\alpha$, $\alpha\beta$, or $\alpha\gamma$), ADH1B ($\beta\beta$ or $\beta\gamma$), and ADH1C ($\gamma\gamma$). Class II contains ADH4 ($\pi\pi$). Class III contains ADH5 ($\chi\chi$). Class IV contains ADH7 ($\mu\mu$ or $\sigma\sigma$). Class V contains ADH6 for which there is no subunit designation ([Parkinson & Ogilvie, 2008](#)).

The low- K_m class I ADHs (α , β and γ subunits, formerly called ADH-1, -2, and -3) account for most of the ethanol-oxidizing capacity in the liver and gastrointestinal mucosa ([Lee et al., 2006](#)). Class I ADH is also expressed in several other tissues, such as the upper and lower digestive tracts ([Yin et al., 1993](#); [Seitz et al., 1996](#); [Yin et al., 1997](#); [Jelski et al., 2002](#)), pancreas ([Chiang et al., 2009](#)), lungs ([Engeland & Maret, 1993](#)), breast ([Triano et al., 2003](#)), blood vessels ([Jelski et al., 2009](#)) and salivary glands ([Visapää et al., 2004](#)). In brain no functionally significant class I ADH has been detected ([Estonius et al., 1996](#)).

Allelic variants have been identified in the *ADH1B* and *ADH1C* genes that encode for the β_1 , β_2 , β_3 , γ_1 , and γ_2 subunits, which can combine as homodimers or can form heterodimers with each other and with the α subunit. ADH1B enzymes that differ in the type of β subunit are known as allelozymes, as are ADH1C enzymes that differ in the type of γ subunit. Allelozymes

Fig. 4.1 Ethanol and acetaldehyde metabolism



ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; CYP, cytochrome P450; CNS, central nervous system; NADPH, nicotinamide-adenine dinucleotide phosphate. Adapted from [Vasilidou et al. \(2004\)](#).

present different kinetic properties ([Table 4.1](#)) and so differ in their capacity to oxidize ethanol. The allelozymes that are homodimers or heterodimers of β_2 subunit (encoded by the *ADH1B*2* allele) are especially active ethanol oxidizing enzymes. The *ADH1B*2* allelic variant is found in 90% of the Pacific Rim Asian population and is responsible for the unusually rapid conversion of ethanol to acetaldehyde in this population. *ADH1B*2* is also more common in people of Jewish origin compared to people of other Caucasian descent (where it is found in 0 to < 20%) ([Neumark et al. 1998](#)). The *ADH1B*1* allele is most common in Caucasians (up to 95%) and *ADH1B*3* is found mostly in African and African Americans (~24%). These population differences in *ADH1B* alloenzyme expression potentially contribute to ethnic differences in alcohol consumption and toxicity. Unlike the *ADH1B* allelozymes, the *ADH1C* variants do not

differ much in their ethanol oxidizing activities ([Parkinson & Ogilvie, 2008](#)).

The class II π -ADH (subunit encoded by *ADH4*) also contributes to hepatic ethanol oxidation, especially at higher concentrations ([Edenberg 2007](#); [Birley et al., 2009](#); [Kimura et al., 2009](#)). *ADH4* expression has been found in most epithelial tissues.

Little is known about the functional role of class III, IV and V ADHs (encoded by the genes *ADH5*, 7 and 6, respectively) in the oxidation of alcohol.

Microbial ADHs

There is a large population of microorganisms present in the gastrointestinal tract that may contribute to ethanol oxidation. Another local site for microbial alcohol oxidation is the oral cavity. Microorganisms express numerous forms of ADH, the role of which may become

Table 4.1 Major allele variants and biochemical properties of human alcohol dehydrogenases (ADHs)

Official nomenclature ^a	Former nomenclature ^b	Additional nonstandard nomenclature ^c	Sequence ^d	Allele	Amino Acid differences between alleles	Protein subunit	Class ^e	K _m (mM) ^f	V _{max} (min ⁻¹) ^g
ADH1A	ADH1		NM_000667	ADH1A		α	I	4.0	30
ADH1B	ADH2		NM_000668	ADH1B*1 ADH1B*2 ADH1B*3	Arg48, Arg370 His48, Arg370 Arg48, Cys370	β1 β2 β3	I	0.05 0.9 40	4 350 300
ADH1C	ADH3		NM_000669	ADH1C*1 ADH1C*2 ADH1C*352Thr	Arg272, Ile350 Gln212, Val350 ^h Thr352	γ1 γ2 NR	I	1.0 0.6 NR	90 40 NR
ADH4	ADH4	ADH2	NM_000670	ADH4*1 ADH4*2		π	II	30	40
ADH5	ADH5	ADH3	NM_000671			X	III	> 1000	100
ADH6	ADH6	ADH5	NM_000672				V	NR	NR
ADH7	ADH7	ADH4	NM_000673			σ or μ	IV	30	1800

^a Nomenclature approved by the Human Genome Organization (HUGO) Gene Nomenclature Committee (www.gene.ucl.ac.uk/nomenclature/), as used by the National Center for Biotechnology Information (NCBI)

^b Former nomenclature

^c Non-standard nomenclature proposed by [Duester et al. \(1999\)](#)

^d Reference sequence number as listed in the NCBI RefSeq database (www.ncbi.nlm.nih.gov/RefSeq/)

^e ADH proteins have been divided into five classes based on sequence and structural similarities

^f V_{max} indicates how many molecules of ethanol the enzyme will convert to acetaldehyde in 1 minute at saturating ethanol concentrations.

^g K_m indicates the concentration of ethanol at which the enzyme works at 50 percent capacity.

^h ADH1C*352Thr has been found in Native Americans as an additional variation on chromosomes with the Val350 characteristics of ADH1C*2 ([Osier et al., 2002](#)); the protein has not been isolated for study. The kinetic constants are noted for the homodimers of the ADH subunits listed (heterodimers behave as if the active sites were independent).

NR, not reported

Adapted from [Edenberg \(2007\)](#)

even more significant wherever microbial overgrowth occurs ([Salaspuro, 2003](#)).

(iii) Cytochrome P450 oxidation pathway

See Fig. 4.1.

Cytochrome P450 2E1 (CYP2E1) is constitutively expressed in the endoplasmic reticulum of the liver and many other tissues including the brain, in contrast to the expression of ADHs. Its K_m for ethanol is about 10 mM; thus CYP2E1 may assume a greater role in the first-order oxidation reaction at high blood-alcohol levels. Other cytochrome enzymes, CYP1A2 and CYP3A4, also contribute to the oxidation of ethanol, albeit to a lesser extent ([Lieber, 2004](#)). CYP2E1 has the unique property of being induced as a result of chronic alcohol intake, which explains part of the increased alcohol elimination rate after chronic alcohol ingestion ([Lieber, 2004](#)). The CYP2E1-mediated ethanol oxidation is associated with nicotinamide-adenine dinucleotide phosphate (NADPH)-CYP reductase in the endoplasmic reticulum, and reduces molecular oxygen to water as ethanol is oxidized to acetaldehyde. CYP2E1 is unusually 'leaky' and generates reactive oxygen species including hydroxyl radical, superoxide anion, hydrogen peroxide and hydroxyethyl radical. Thus, CYP2E1 is a major source of alcohol-related oxidative stress ([Caro & Cederbaum, 2004](#)).

Genetic variants of CYP2E1

Several allele variants of CYP2E1 have been described in humans (see [Table 4.2](#)).

The allele variant commonly denoted as c2, CYP2E1*5B according to the new recommended nomenclature, has been found more frequently in East Asian individuals (~40%) compared with Caucasians (~8%) ([Garte et al., 2001](#)). Early studies showed an increased CYP2E1 expression and activity in ethanol oxidation associated with the *5B allele ([Hayashi et al., 1991](#); [Tsutsumi et al., 1994](#); [Watanabe et al., 1994](#)), but this finding has not been confirmed in other studies ([Carrière](#)

[et al., 1996](#); [Kim et al., 1996](#); [Powell et al., 1998](#); [Kato et al., 2003](#)), and contrasting results have been reported ([Huang et al., 2003](#)). So it is unclear to what extent the functional activities regarding ethanol oxidation differ from those of the corresponding wild types. Other variants of CYP2E1 polymorphisms, such as CYP2E1*6, have also been shown to be more common in East Asians (ca. 52%) compared with Caucasian individuals (ca. 15%) ([Garte et al., 2001](#)).

(iv) Ethanol oxidation by catalase (Fig. 4.1)

Catalase is constitutively expressed in the peroxisomal part of the endoplasmic reticulum in virtually all tissues. It is an important antioxidant enzyme that detoxifies H_2O_2 into oxygen and water and thus limits the deleterious effects of reactive oxygen species. The functional role of catalase in the oxidation of ethanol in humans is not known. Although catalase-mediated ethanol oxidation is very limited compared with ADH-mediated reactions, it may play a significant role in specific organs and tissues that lack the functional ADH. Based on experimental animal research, catalase seems to contribute to alcohol oxidation in the brain ([Cohen et al., 1980](#); [Zimatkin et al., 2006](#)). As with CYP2E1, catalase also has a high K_m and, thus, the impact on alcohol oxidation would be higher at high alcohol levels. No functional polymorphism regarding alcohol oxidation or its effects has been reported.

(v) Non-oxidative ethanol metabolism

Ethanol can be non-oxidatively metabolized to form fatty-acid ethyl esters (FAEEs), which are toxic for cells ([Laposata & Lange, 1986](#); [Laposata et al., 2002](#)). These esters are formed during the hydrolysis of fatty-acid esters (e.g. triglycerides) in the presence of ethanol. Such esterification activity has been detected in humans mainly with the two high- K_m enzymes fatty-acid ethyl ester synthases (FAEEs) ([Wright et al., 1987](#)) and acyl-coenzyme A:ethanol O-acyltransferase (AEAT) ([Diczfalusy et al., 2001](#)). Highest activities have

Table 4.2 Major allelic variants and biochemical properties of humans cytochrome P450 2E1 (CYP2E1)

Recommended nomenclature ^a	Alternative nomenclature ^a	Protein	Nucleotide changes, Gene	RFLP	Effect	Enzyme activity	
						<i>In_vivo</i>	<i>In_vitro</i>
CYP2E1*1A	CYP2E1*1	CYP2E1.1	None			Normal	Normal
CYP2E1*1B	CYP2E1*2	CYP2E1.1	9896C > G	<i>TaqI</i> -			
CYP2E1*1C	CYP2E1.1	CYP2E1.1	6 repeats in the 5' flanking region				
CYP2E1*1D	CYP2E1.1	CYP2E1.1	8 repeats in the 5' flanking region	<i>DraI</i> and <i>XbaI</i>		Incr. activity after alcohol exposure and in obese subjects	
CYP2E1*2	CYP2E1.2	CYP2E1.2	1132G > A		R76H	Reduced	
CYP2E1*3	CYP2E1.3	CYP2E1.3	10023G > A		V389I	Normal	
CYP2E1*4	CYP2E1.4	CYP2E1.4	4768G > A		V179I	Normal	
CYP2E1*5A	CYP2E1.1	CYP2E1.1	-1293G > C; -1053C > T (c1 > c2); 7632T > A	<i>PstI</i> + <i>RsaI</i> - <i>DraI</i> -			
CYP2E1*5B	CYP2E1*3	CYP2E1.1	-1293G > C; -1053C > T (c1 > c2)	<i>PstI</i> + <i>RsaI</i> -			
CYP2E1*6	CYP2E1*4	CYP2E1.1	7632T > A	<i>DraI</i> -			
CYP2E1*7A	CYP2E1.1	CYP2E1.1	-333T > A				
CYP2E1*7B	CYP2E1.1	CYP2E1.1	-71G > T; -333T > A				
CYP2E1*7C	CYP2E1.1	CYP2E1.1	-333T > A; -352A > G				
not included	CYP2E1*5						
not included	CYP2E1*6						

^a Two different nomenclature systems were developed for the CYP2E1 alleles simultaneously. The authors of both nomenclature systems have agreed in July 2000 that the nomenclature system given in the first column should be the recommended one, see [Ingelman-Sundberg et al. \(2001\)](#); the other nomenclature that was proposed by [Garte & Crosti \(1999\)](#) is given in the second column.

RFLP, restriction fragment length polymorphism

Adapted from <http://www.cypalleles.ki.se/cyp2e1.htm>

been located in the liver and pancreas, and in the liver and duodenum, for FAEs and AEAT, respectively ([Diczfalusy et al., 2001](#)). Lower activities of both enzymes were found in heart, lung, adipose, gall bladder and gastric tissues. Although FAE may be important in the etiology of alcohol-mediated cellular toxicity, especially in the case of long-term accumulation during chronic alcohol intake, the relative contribution to overall alcohol elimination is rather small. In addition to FAEs, alcohol also forms other conjugates, such as ethyl glucuronide, often used as a marker for recent alcohol drinking ([Wurst et al., 2003](#)).

4.1.2 Acetaldehyde

Acetaldehyde is the first metabolite in the oxidation of ethanol (Fig. 4.1). Interindividual variations of the acetaldehyde-mediated effects will depend on the genetic polymorphisms and other factors affecting the metabolism and levels of acetaldehyde, and the effects on the target organs.

(a) Origin of acetaldehyde

(i) Endogenous formation

Several degradation reactions are known to form endogenous acetaldehyde in the human body ([Krebs & Perkins, 1970](#)). Without external alcohol ingestion, acetaldehyde concentrations are below the level of detection, except in the gastrointestinal tract ([Väkeväinen et al., 2000](#)). However, under conditions of inhibited acetaldehyde-oxidation capacity, endogenous acetaldehyde levels may be detected in the blood ([Eriksson, 1985](#)). The relevance of the endogenous acetaldehyde is further discussed in Section 4.3.1.

(ii) Acetaldehyde in alcoholic beverages

A small part of the total acetaldehyde to which the body is exposed comes directly from ingested alcoholic beverages. All alcoholic beverages

contain acetaldehyde in variable amounts: average levels in different types vary between 60 to > 7000 μM ([Lachenmeier & Sohnius, 2008](#)). The magnitude and the significance of exposure to acetaldehyde from alcoholic beverages are further discussed in Section 4.3.1.

(iii) Acetaldehyde formation by oxidation of exogenous ethanol

The major part of the total acetaldehyde to which the body is exposed during alcohol ingestion originates from ethanol oxidation catalysed by the ADH, CYP2E1 and catalase enzymes. The liver and the gut are the primary sites of acetaldehyde formation to such an extent that the rate of alcohol oxidation exceeds the rate of acetaldehyde breakdown, which consequently leads to diffusion of the surplus acetaldehyde into the bloodstream. Under normal conditions, i.e. without reduced capacity for acetaldehyde oxidation or considerably increased acetaldehyde formation, the acetaldehyde produced at other sites is usually directly oxidized within the tissue. The exception is the aerodigestive tract, where acetaldehyde is produced at least partly by microbial alcohol oxidation. Consequently, acetaldehyde can be detected both in breath and saliva during alcohol intoxication ([Eriksson, 2007](#)).

(b) Metabolism

The bulk of the acetaldehyde formed in the liver is directly oxidized by NAD^+ -dependent aldehyde dehydrogenases (ALDHs) to acetate. The efficacy of normal hepatic oxidation of the alcohol-derived acetaldehyde is estimated to be close to 99% ([Eriksson & Fukunaga, 1993](#)). In addition, a minor part of the acetaldehyde is probably oxidized by aldehyde oxidase and CYP2E1. In addition, acetaldehyde reacts with a variety of chemical compounds in the body.

(i) Aldehyde dehydrogenase pathway

Acetaldehyde is metabolized by ALDHs (Fig. 4.1), which are widely expressed in the mitochondria (low- K_m enzyme) and cytosol (high- K_m enzyme) of most tissues (Crabb, 1995). Oxidation of acetaldehyde is regulated by the rate of acetaldehyde formation, ALDH activity and the cytosolic and mitochondrial redox states. Ethanol consumption is not known to induce *ALDH* expression. Chronic alcohol abuse, especially associated with liver disease, has been reported to reduce the ALDH activity (Nuutinen *et al.*, 1983).

The major allelic variants of human ALDHs, their respective K_m and their ethnical distribution are summarized in Table 4.3. The high- K_m ALDH1A1 accounts for most of the acetaldehyde-oxidizing capacity in the cytosolic compartment of the liver and other tissues. This enzyme is also abundant in the erythrocytes. Several variant alleles of *ALDH1A1* with potential functional relevance have recently been reported in the promoter (Spence *et al.*, 2003), intron and untranslated regions (Lind *et al.*, 2008) (Table 4.1).

The low- K_m (about 5 μ M for acetaldehyde) ALDH2 is located in the mitochondria and is believed to be responsible for the bulk of the oxidation of the ethanol-derived acetaldehyde. This enzyme is not significantly expressed in the erythrocytes. Of all the polymorphisms in genes encoding enzymes that metabolize alcohol and acetaldehyde, the *ALDH2**2 allele has the greatest functional impact on the human phenotype. This allele is common in East-Asian populations, about 5–10% homozygotes and 30–40% heterozygotes (Brennan *et al.*, 2004). In these individuals the acetaldehyde levels are elevated, which creates several toxic effects and also euphoric reinforcing reactions (Eriksson, 2001). The relevance of the elevated acetaldehyde for the development of cancers is discussed in section 4.3.1. In addition to the *2 allele, promoter-region

variants have been reported (Harada *et al.*, 1999). The functional significance of these other variants remains to be established. The relevance of other ALDHs, including ALDH1B1 and other classes of ALDH, also remains to be elucidated.

(ii) Other pathways in the metabolism and reactions of acetaldehyde

In addition to the ALDH-catalysed reactions, acetaldehyde may also be oxidized to a minor extent by CYP2E1 (Terelius *et al.*, 1991) and by different oxidases (Deitrich *et al.*, 2007).

Due to its chemical reactivity, most, if not all, of the ethanol-derived acetaldehyde that is not further oxidized binds to a variety of constituents. These interactions vary between easily reversible and firm covalent bonds. Different kinds of Schiff's base, which are formed by acetaldehyde and the free amino groups of amino acids, peptides and proteins, are the most common products (Eriksson & Fukunaga, 1993, Niemelä, 2007). Some of these unstable products become stable under reducing conditions, such as during alcohol intoxication. Although only a small fraction of all acetaldehyde formed during ethanol oxidation produces these adducts, they are important in some of the chronic toxic actions of alcohol. The role of the acetaldehyde adducts in the carcinogenic effects of alcohol is further discussed in Sections 4.2.2, 4.3.1 and 4.4.2.

(c) Levels of acetaldehyde in tissues

From the liver, where most of the ethanol-derived acetaldehyde is formed and oxidized, the remaining acetaldehyde, free and/or loosely bound, escapes into the *vena hepatica*, reaching concentrations of approximately 70 μ M under normal conditions (Eriksson & Fukunaga, 1993). Thereafter, the concentration of acetaldehyde in the blood will be diluted by the *vena cava* blood and further reduced by the circulation in the heart and the lungs before reaching peripheral tissues. Human data show that acetaldehyde levels in pulmonary arterial blood are in the

Table 4.3 Major allelic variants, biochemical properties, and ethnical distribution of human acetaldehyde dehydrogenases (ALDHs)

Gene Locus	Allele	Km μM^a	Ethnic/national distribution ^b	References
<i>ALDH1A1</i>		50	All	Vasiliou et al. (2000)
<i>ALDH2</i>	<i>ALDH2*1</i>	< 5	All	
	<i>ALDH2*2</i>		Asia	Crabb et al. (1989)
	<i>ALDH2*3</i>		Taiwan, People's Republic of China	Novoradovsky et al. (1995)
<i>ALDH1B1</i>	<i>ALDH1B1*1</i>	NR		
(<i>ALDH5</i>)	<i>ALDH1B1*2</i>	NR		Sherman et al. (1993)
<i>ALDH9A1</i>	<i>ALDH9A1*1</i>	30	All	Kurys et al. (1989)
	<i>ALDH9A1*2</i>			Lin (1996)

^a Kinetic constant of the enzyme when acetaldehyde is the substrate

^b The column labelled ethnic/national distribution indicates which populations have high allele frequencies for these variants. The alleles are not limited to those populations.

NR, not reported

Compiled by the Working Group

range of 0–4.4 μM , 30 and 60 minutes after ethanol consumption ([DeMaster et al., 1983](#)) during normal alcohol oxidation. Acetaldehyde in peripheral arterial or venous blood is below the limit of detection (< 1 μM) during normal alcohol intoxication in Caucasian male populations ([Eriksson & Fukunaga, 1993](#)). However, in Caucasian women, acetaldehyde levels of 1–8 μM have been detected during the use of oral contraceptives and during the high-estradiol phase of the normal cycle ([Eriksson et al., 1996](#)).

Except for the blood and the liver, in which acetaldehyde concentration should be approximately the same as in the *vena hepatica*, little is known about acetaldehyde levels in other tissues during normal alcohol oxidation in humans. Acetaldehyde levels should rise in tissues where the ethanol oxidation rate exceeds the capacity of acetaldehyde oxidation. Breath acetaldehyde concentrations of 10–20 and 20–40 nM at blood alcohol levels of about 10 and 20 mM, respectively, imply corresponding tissue acetaldehyde levels of 2–8 μM in the respiratory tract ([Jones, 1995](#); [Eriksson, 2007](#)). Part of this acetaldehyde is derived by microbial ethanol oxidation ([Pikkarainen et al., 1980](#)). Also, acetaldehyde levels in the saliva, which almost exclusively

are derived from microbiological alcohol oxidation, correlate positively with the blood alcohol concentration ([Väkeväinen et al., 2001](#); [Eriksson, 2007](#)). Levels varying between 15 to 25 μM and 20 to 40 μM at corresponding blood ethanol concentrations of 10 to 20 mM, respectively, have been reported ([Homann et al., 1997](#); [Eriksson, 2007](#)). The role of the acetaldehyde concentrations in the upper aerodigestive tract in the carcinogenic effects of alcohol is discussed in Section 4.3.1.

Under certain conditions, such as chronic alcohol consumption especially in combination with increased alcohol oxidation rate and/or liver disease and genetically determined deficiency in the ALDHs, acetaldehyde levels are considerably elevated. Peripheral venous blood acetaldehyde concentrations of 14 μM have been detected during alcohol intoxication (after a dose of 0.8 g per kg) in alcoholics ([Nuutinen et al., 1984](#)). In Asian subjects carrying the *ALDH2* allele, blood acetaldehyde levels above 200 μM have been reported ([Eriksson & Fukunaga, 1993](#)). In addition to *ALDH2* polymorphism, the *ADH1B*2* and *ADH1C*1* variant alleles, which encode more active ADHs, in turn may elevate ethanol-derived acetaldehyde levels. This possibility was suggested by [Visapää et al. \(2004\)](#) who

reported increased acetaldehyde concentrations in saliva of individuals with the *ADH1C*1/*1* genotype. The relevance of the *ALDH* and *ADH* genotypes for the etiology of cancer is further discussed in Section 4.3.1.

4.2 Genotoxicity

4.2.1 Humans

Studies of genotoxic effects of alcoholic beverages have been reviewed ([Obe & Anderson, 1987](#); [IARC, 1988, 2010](#)).

(a) Genotoxic effects in alcoholics

[Maffei et al. \(2000, 2002\)](#) and [Castelli et al. \(1999\)](#) found that alcoholics had significantly more chromosomal aberrations and cells with micronuclei than either non-drinking controls or abstinent alcoholics. The three groups were matched for age, sex and smoking ([Maffei et al., 2002](#)). When centromeric fluorescence in situ hybridization (FISH) was combined with the analysis of micronuclei, the alcoholics showed an increase in the number of lymphocytes with centromere-positive micronuclei, indicating an elevated formation of micronuclei harbouring whole chromosomes, ie, an aneugenic effect ([Maffei et al., 2000](#)). In a combined analysis of three biomonitoring studies, [Iarmarcovai et al. \(2007\)](#) observed a small but significant increase in micronucleus frequency in alcoholic beverage users compared with controls (OR, 1.24; 95%CI: 1.01–1.53).

While the majority of published studies showed no increase in chromosomal alterations in alcoholics following abstinence from ethanol compared to non-drinkers, some studies reported positive results ([De Torok, 1972](#); [Matsushima, 1987](#)). [Gattás & Saldanha \(1997\)](#) compared the frequency of structural or numerical chromosomal aberrations in lymphocytes of alcoholics who had been abstinent for 1 month to 32 years, with those in subjects not consuming alcoholic

beverages. They noted a significant increase in the frequency of cells with structural chromosomal aberrations in the abstinent alcoholics. [Burim et al. \(2004\)](#) observed that the frequencies of chromosomal aberrations in lymphocytes of 29 chronic alcoholics and 11 alcoholics in abstinence were higher than those in 10 control individuals. The level of chromosomal aberrations was not statistically significantly different when smoking and non-smoking alcoholics were compared, which indicated a lack of interaction.

There is some indication that ethanol may lead to chromosomal aneuploidy in human sperm. [Robbins et al. \(1997\)](#) used FISH of the sex chromosomes and chromosome 18 to investigate the potential contribution of common lifestyle exposures to aneuploidy load in sperm from 45 healthy male volunteers. Consumption of alcoholic beverages was significantly associated with increased frequencies of aneuploidy XX18, XY18–18 apparent diploidy, or XX18–18 duplication phenotype, after controlling for caffeine, smoking and donor age.

[Härkönen et al. \(1999\)](#) reported a significant negative association between alcohol intake and sperm aneuploid for chromosomes 1 and 7 (1-1-7 and 1-7-7 constitutions and diploid sperm) among 30 agricultural workers before pesticide exposures, while no statistically significant findings were related to alcohol intake after the exposure. [These inconclusive findings may reflect moderate alcohol consumption (average 6 drinks/week).]

In a case-control study [Kagan-Krieger et al. \(2002\)](#) found no association between self-reported paternal or maternal alcohol consumption and Turner syndrome in offspring.

[Pool-Zobel et al. \(2004\)](#) used the comet assay to study DNA damage and repair in human rectal cells obtained from biopsies and found that male alcoholic beverage abusers had significantly less DNA strand-breaks than male controls. This may be the result of an enhancing effect on endogenous defence, e.g. through upregulation of DNA

repair in response to damage. [Alternatively, a reduced amount of DNA in the comet tails could reflect DNA–protein crosslinks resulting from exposure to endogenous acetaldehyde.]

[van Zeeland et al. \(1999\)](#) and [Lodovici et al. \(2000\)](#) did not detect any increase in 8-hydroxydeoxyguanosine (8-OHdG) levels [measure of oxidative DNA damage] in leukocyte DNA in relation to alcoholic beverage consumption. In a multicentre study in Europe, [Bianchini et al. \(2001\)](#) observed an inverse relationship between alcoholic beverage consumption and levels of 8-OHdG in leukocyte DNA. However, an increased level of 8-OHdG in leukocyte DNA was observed in ALDH2-deficient subjects who consumed alcoholic beverages ([Nakajima et al., 1996](#)).

[Frank et al. \(2004\)](#) reported a significant increase in 1,N⁶-ethenodeoxyadenosine DNA adducts in seven subjects diagnosed with alcoholic fatty liver and three diagnosed with alcoholic fibrosis. Patients with alcoholic fibrosis had a much higher level of these adducts than patients with alcoholic fatty liver. [No diagnostic criteria were provided for patients identified as ‘alcoholic’.]

[Wanget al. \(2009\)](#) observed that protein-bound 4-hydroxynonenal [a major lipid peroxidation product] and both 1,N⁶-ethenodeoxyadenosine and 3,N⁴-ethenodeoxycytidine DNA adducts strongly correlated with CYP2E1 expression in fine-needle liver biopsy samples obtained from 14 German patients with alcoholic liver disease ($r = 0.97$, $P < 0.01$). [The results support the assumption that, particularly in non-Asian populations, ethanol-mediated induction of hepatic CYP2E1, leading to highly miscoding DNA lesions derived from lipid peroxidation, may play a central role in hepatocarcinogenesis in patients with alcoholic liver disease.]

A statistically significantly higher frequency of sister chromatid exchange in lymphocytes was observed in Japanese subjects deficient in ALDH2 (at least one *2 allele) compared to those

who were proficient in ALDH2 (*1/*1 genotype) and drank alcohol almost daily; such an effect was not seen in subjects who drank less or did not drink at all ([Morimoto & Takeshita, 1996](#)).

(b) *Effects of polymorphisms for metabolic enzymes*

A significant difference in micronucleus frequency between the ALDH2*2 allele carriers and the individuals carrying the ALDH2*1/*1 genotype was found at all levels of alcohol consumption; the highest micronucleus levels were seen in the ALDH2*2 allele carriers consuming more than 100 g of alcohol per week and more than 3 times a week ([Ishikawa et al., 2003](#)).

In non-smoking regular or occasional Japanese drinkers, the frequency of micronuclei was shown to be higher in ALDH2*2/*2 homozygotes versus ALDH2*2/*1 heterozygotes and in ADH1B*1/*1 homozygotes versus ADH1B*1/*2 heterozygotes. The highest micronucleus levels were seen in regular drinkers carrying both the ALDH2*2 and ADH1B*1 alleles. Nonetheless, due to the low number of subjects, a statistically significant increase of micronuclei was only seen for regular drinkers who carry the more common combination, i.e. ALDH2*2 and ADH1B*2 alleles ([Ishikawa et al., 2007](#)).

Regular drinkers with the CYP2E1*1/*1 genotype showed a significantly higher micronucleus frequency than drinkers carrying the CYP2E1*3 allele; and drinkers with combined ALDH2*2 and CYP2E1*1/*1 genotypes showed the highest micronucleus frequency ([Ishikawa et al., 2006](#)).

4.2.2 *Experimental systems*

(a) *Ethanol*

The genotoxic potential of ethanol has been extensively evaluated in lower organisms, plants, mammalian systems and in human cells, as reviewed previously ([IARC, 1988, 2010](#); [Phillips & Jenkinson, 2001](#)).

Ethanol gave negative results in bacterial mutagenicity tests, even in the presence of exogenous metabolic activation systems. These findings are consistent with the negative findings obtained with acetaldehyde, the primary *in vivo* metabolite of ethanol, in bacterial genotoxicity assays ([IARC, 2010](#)).

Positive results were reported for the induction of DNA strand breaks and chromosome malsegregation by ethanol in fungi and sister chromatid exchange in plants without exogenous metabolic activation. [These findings were obtained at very high concentrations (16000–39100 µg/ml) exceeding those usually recommended as the highest allowable concentrations in genotoxicity testing.]

In mammalian cells *in vitro*, ethanol was not usually able to produce gene mutations or chromosomal aberrations, but one study in mouse preimplantation embryos *in vitro* showed an induction of sister chromatid exchanges and chromosomal aberrations. In these experiments, sister chromatid exchange disappeared in the presence of 4-methylpyrazole, an inhibitor of alcohol dehydrogenase. This suggests that preimplantation embryos are able to convert ethanol to acetaldehyde.

A single study reported ethanol-induced DNA strand breaks in various types of human cells ([Blasiak et al., 2000](#)). The majority of studies showed no induction of chromosome damage by ethanol in human lymphocytes and lymphoblastoid cells *in vitro*. [The Working Group noted that in most of the *in vitro* genotoxicity studies, external metabolic activation systems were not used, which reduces the value of the negative findings.]

Ethanol induced micronuclei in human lymphoblastoid cells without external metabolic activation ([Kayani & Parry, 2010](#)). This effect appeared to be independent of acetaldehyde, since the micronuclei mostly contained whole chromosomes, while those induced by acetaldehyde harboured chromosomal fragments. Thus,

ethanol produced micronuclei *in vitro* by an aneugenic mechanism while acetaldehyde was clastogenic.

In animals *in vivo*, ethanol induced DNA adducts, DNA strand breaks, and sister chromatid exchanges and dominant lethal mutations. No effect of ethanol was seen in the micronucleus or chromosome aberration assays *in vivo*. In rats, exposure to ethanol increased mitochondrial DNA (mt DNA) oxidation and decreased the amount of mt DNA ([Cahill et al., 1997, 2005](#)). Several studies showed that the administration of ethanol to rats and mice leads to changes in the activity and amount of DNA-repair proteins in the liver ([Navasumrit et al., 2001a](#); [Bradford et al., 2005](#)).

The ethanol-induced DNA single-strand breaks in liver parenchymal cells of rat closely matched the timing of CYP2E1 induction and was inhibited by dietary antioxidants ([Navasumrit et al., 2000](#)). Ethanol also increased the level of the lipid peroxidation-derived DNA adduct, ethenodeoxycytidine in rats ([Navasumrit et al., 2001b](#)) and *N*²-ethyl-2'-desoxyguanosine (*N*²EtdG) adducts, not detectable in controls, were seen in liver DNA of ethanol-treated mice ([Fang & Vaca, 1995](#)). Rats and mice fed ethanol showed increased levels of oxidative DNA damage (abasic sites and 8-hydroxydeoxyguanosine) in the liver ([Bradford et al. 2005](#)); this effect was observed in transgenic mice that expressed human CYP2E1, but not in CYP2E1-knockout mice or in the presence of a CYP2E1 inhibitor. Increased levels of 1,*N*⁶-ethenodeoxyadenosine and 3,*N*⁴-ethenodeoxycytidine DNA adducts (measured by immunohistochemistry) were observed in the liver of ethanol-fed lean (Fa/Fa) and obese (fa/fa) Zucker rats ([Wang et al., 2009](#)). The number of hepatocyte nuclei that stained positively for these etheno-DNA adducts correlated significantly with CYP2E1 expression.

(b) Acetaldehyde

Numerous *in vitro* studies have consistently shown that acetaldehyde causes DNA–protein crosslinks, DNA strand breaks, DNA adducts, sister chromatid exchanges, chromosomal aberrations, and micronuclei in eukaryotic cells *in vitro* (Speit *et al.*, 2008; Kayani & Parry, 2010; IARC, 2010). In comparison with other assays, the comet assay requires relatively high concentrations of acetaldehyde to show a positive result, probably reflecting the formation of crosslinks (Speit *et al.*, 2008).

Acetaldehyde induced also DNA protein crosslinks, sister chromatid exchanges, and chromosomal aberrations in rodents *in vivo* (IARC, 2010).

4.2.3 Genotoxicity of acetaldehyde

(a) DNA adduct formation

The structure of acetaldehyde-derived DNA adducts is depicted in Fig. 4.2.

(i) *N*²-Ethyl-2'-deoxyguanosine (*N*²EtdG)

The most abundant DNA adduct that results from the reaction of acetaldehyde is *N*²-ethylidenedeoxyguanosine (*N*²EtidG). This adduct is too unstable to be purified and isolated, but can be converted into the stable adduct *N*²EtdG, by treatment with a reducing agent (sodium cyanoborohydride). The reduction step can also be carried out by a mixture of GSH and ascorbic acid, which may occur *in vivo* (Fang & Vaca, 1995; Wang *et al.*, 2006c).

Fang & Vaca (1997) examined the levels of the *N*²EtdG adduct in a group of Swedish alcohol abusers compared to controls. They found that chronic alcoholics had higher levels of the *N*²EtdG adduct in both lymphocytes and granulocytes compared with controls. The levels of adduct found in both cell types were on the order of one lesion/10⁷ nucleotides. [The Working Group noted that the alcoholic subjects were also heavy smokers, whereas the control subjects were

not. However, the authors reported that *N*²EtdG levels were undetectable in the DNA sample from the one moderate smoker in the control group, and also stated that no adducts were detectable in samples obtained from five additional heavy smokers (> 20 cigarettes/week)].

Inclusion of a reducing agent (cyanoborohydride) in the DNA isolation and digestion solutions allowed *N*²EtidG to be converted quantitatively to *N*²EtdG. Wang *et al.* (2006c) concluded that *N*²EtidG is in fact an endogenous DNA adduct that is present in every animal and human liver DNA at levels in the range of 0.1 lesion/10⁶ normal nucleotides.

Balbo *et al.* (2008) measured the level of *N*²-EtdG in blood leukocyte DNA of two groups of subjects, one consisting of alcohol drinkers and abstainers and the other of heavy drinkers. A significant trend between *N*²-EtdG level and daily alcohol dose was found. In the first group, the mean level of *N*²-EtdG was significantly higher in drinkers (5270 ± 8770 fmol/μmol dG) than in non-drinkers (2690 ± 3040 fmol/μmol dG; *P* = 0.04) after adjusting for potential confounders. Taking into account the dose, the adduct level was higher in younger than older drinkers.

Matsuda *et al.* (1999) reported that detectable levels of *N*²EtdG were found in the urine of healthy Japanese individuals who had abstained from ethanol for at least 1 week. These authors proposed that the lesion resulted from endogenously formed acetaldehyde.

(ii) Other acetaldehyde-derived DNA adducts

In addition to the major adduct *N*²EtidG, three acetaldehyde-derived DNA adducts have been identified. These are: *N*²-(2,6-dimethyl-1,3-dioxan-4-yl) deoxyguanosine (*N*²-Dio-dG); an interstrand crosslink, and two diastereoisomers (R and S) of α-methyl-γ-hydroxy-1,*N*²-propanodeoxyguanosine (α-Me-γ-OH-PdG) (Wang *et al.*, 2000).

[Matsuda et al. \(2006\)](#) analysed the levels of acetaldehyde-derived DNA adducts in DNA samples from peripheral white blood cells of Japanese alcoholic beverage abusers with two different *ALDH2* genotypes: *1/*1 versus *1/*2. The groups were matched by age, smoking and alcoholic beverage consumption. These authors developed very sensitive and specific liquid chromatograph–mass spectrometry assays for the DNA adducts: *N*²EtdG, α -Me- γ -OH-PdG (both R and S isomers) and *N*²-Dio-dG. The *N*²-Dio-dG adduct was not detected in any of the samples studied. Levels of the other three adducts were significantly higher in *1/*2 carriers than in *1/*1 genotypes.

The formation of the methyl-hydroxypropano-dG adducts can be facilitated by including basic amino acids, histones (which are rich in basic amino acids), or polyamines in the reaction mixture. In the presence of physiologically relevant polyamine concentrations, detectable amounts of these adducts were formed from concentrations as low as 100 μ M acetaldehyde ([Theruvathu et al., 2005](#)). Such concentrations are within the range of acetaldehyde concentrations formed in the saliva of human volunteers who drank alcoholic beverage in a laboratory setting ([Homann et al., 1997](#)). Finally, acetaldehyde can react with malondialdehyde, and the resulting conjugate can form DNA adducts *in vitro* ([Pluskota-Karwatka et al., 2006](#)).

(b) Mutagenicity of acetaldehyde-derived DNA adducts

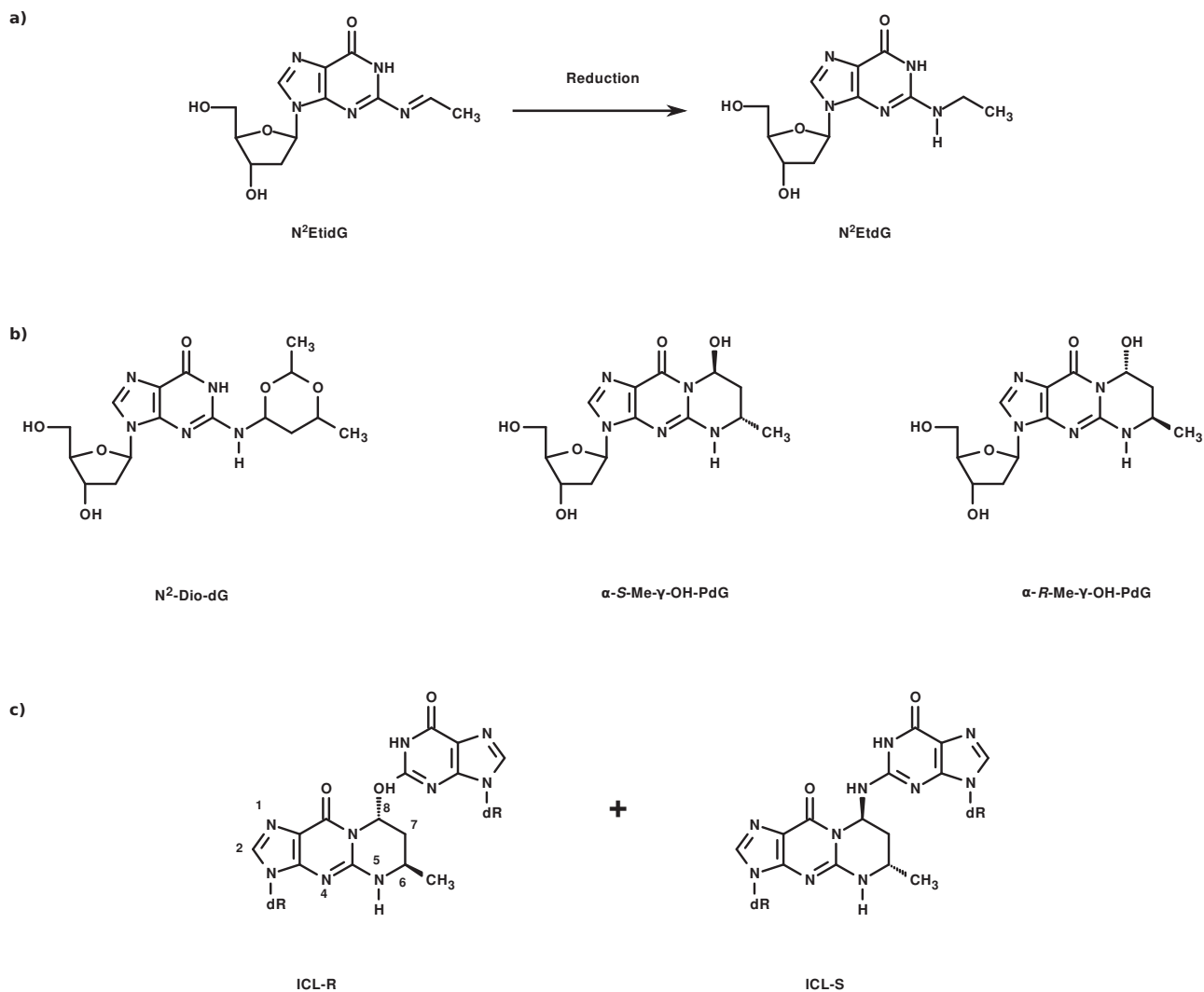
The mutagenic potential of DNA adducts can be tested with single-stranded DNA vectors that contain a single adduct located within a reporter gene. These constructs can then be transfected into cells, allowed to replicate and the resulting replication products analysed for mutations in various ways, depending on the specific nature of the reporter gene. Using such an approach, the *N*²EtdG adduct was only minimally mutagenic to the *supF* gene in the reporter plasmid

pLSX (mean mutant fraction, $0.9 \pm 0.2\%$ for the adduct-containing construct versus $0.4 \pm 0.2\%$ for the lesion-free control) when replicated in *E. coli* ($P = 0.09$). When deoxyuridines were placed on the complementary strand at 5' and 3' positions flanking the adduct, the mutant fractions increased to $1.4 \pm 0.5\%$ for the lesion versus $0.6 \pm 4\%$ for the control ($P = 0.04$) ([Upton et al., 2006](#)). The mutation spectrum generated by the *N*²EtdG adduct included mainly G to T transversions and single base deletions three bases downstream from the adduct. [This study was carried out with *N*²EtdG, whereas, *in vivo*, most probably *N*²EtidG is formed predominantly.]

Two separate studies have shown that methylhydroxypropano-dG adducts result in mutant fractions of 5–11% when inserted into a shuttle vector and replicated in either monkey kidney cells ([Fernandes et al., 2005](#)) or human xeroderma pigmentosum A (XPA) cells ([Stein et al., 2006](#)). In both cases, the predominant mutagenic event observed was a G to T transversion, but G to A and G to C mutations were also found. In comparison, the ethenodeoxyadenosine adduct resulted in mutant fractions as high as 70% in COS7 monkey kidney cells ([Pandya & Moriya, 1996](#)), but the mutant fraction was only 7–14% in human cells ([Levine et al., 2000](#)). [Methodological differences, differences in the host cells used or in the local sequence in the shuttle vectors may be responsible for the results.]

An important feature of the methylhydroxypropano-dG adducts, which is not shared by *N*²EtidG or *N*²EtdG, is that these adducts can undergo ring-opening when located in double-stranded DNA ([Mao et al., 1999](#)). The ring-opened forms of the methylhydroxypropano-dG adducts can react with proteins to generate DNA–protein crosslinks ([Kurtz & Lloyd, 2003](#)). With a deoxyguanosine residue in the opposite strand of the helix, a DNA-intrastrand crosslink can be formed ([Wang et al., 2000](#)). Intrastrand crosslinks generated in this manner are also mutagenic (mutant fraction 3–6%) in mammalian cells, generating

Fig. 4.2 Structure of acetaldehyde-derived DNA adducts



a) The immediate reaction of acetaldehyde with DNA is the unstable Schiff base adduct, N^2 -ethylidene-2-deoxyguanosine ($N^2\text{EtdG}$). This adduct is reduced into the more stable N^2 -ethyl-2-deoxyguanosine ($N^2\text{EtdG}$), the most abundant acetaldehyde-derived DNA adduct.

b) Three additional acetaldehyde-derived DNA adducts: N^2 -(2,6-dimethyl-1,3-dioxan-4-yl) deoxyguanosine ($N^2\text{-Dio-dG}$) and the two diastereoisomers (R and S) of α -methyl-8-hydroxy-1, N^2 -propanodeoxyguanosine ($\alpha\text{-Me-}\gamma\text{-OH-PdG}$).

c) Structure of R and S interstrand crosslinks (ICL-R) and (ICL-S).

Adapted from Wang *et al.* (2006c) and Matsuda *et al.* (2006).

primarily G to T transversions, as well as deletion and insertion mutations (Liu *et al.*, 2006). Matsuda *et al.* (1998) exposed plasmid DNA that contains a *supF* mutation reporter gene to acetaldehyde concentrations up to 1M, and allowed the plasmid to replicate in human XPA cells, which are deficient in nucleotide excision repair. In contrast to the results for the methylhydroxypropano-dG adducts, these authors observed specific tandem GG to TT mutations. The DNA lesions responsible for these mutations are most probably not propano-dG adducts, but the intrastrand crosslinks.

4.3 Synthesis: Mechanistic considerations

Although alcoholic beverages may contain several potentially carcinogenic compounds, this synthesis focuses on the role of ethanol and acetaldehyde in the carcinogenesis associated with alcoholic beverages.

4.3.1 Ethanol-related mechanisms of carcinogenesis

The role of ethanol metabolism in tumour initiation is implied by the associations observed between different forms of cancer and polymorphisms in genes involved in the oxidation of ethanol. Whether, or to what degree, these associations are explained by redox changes, formation of radicals, effects on intermediary metabolism and/or effects on other pro-carcinogens cannot be established from current findings.

(a) Oxidative stress

Ethanol-induced CYP2E1 produces various reactive oxygen species, which lead to the formation of lipid peroxidation products such as 4-hydroxy-nonenal and the condition of oxidative stress. Chronic tissue inflammation and increased iron content exacerbate these actions. The increased reactive oxygen species

and oxidative stress, which damage the DNA and affect its repair, has been associated with ethanol-induced carcinogenesis in many organs, such as the breast, liver and pancreas.

(b) Cirrhosis

Ethanol causes hepatocellular injury that can lead to enhanced fibrogenesis and finally cirrhosis. Liver cirrhosis is strongly associated with an increased risk for developing hepatocellular carcinoma. Ethanol-related hepatocellular carcinoma without pre-existing cirrhosis is rare, which indicates that the pathogenic events that lead to cirrhosis precede those that cause cancer, or that the structural alterations in the liver during cirrhosis, together with other factors, favour the transformation of hepatocytes.

(c) Interaction between alcohol and tobacco smoking

This aspect is discussed in Section 4 of the *Monograph* on Tobacco Smoking in this Volume.

(d) Ethanol and sex hormones

Estrogens and androgens are well known activators of cellular proliferation, which is associated with an increased risk for carcinogenesis. Alcoholic beverage consumption in women causes an increase in the levels of estrogen and androgen, which has been suggested to contribute to the development of breast cancer. ADH-mediated alcohol oxidation, which increases the hepatic redox state, which in turn inhibits catabolism of sex steroids, has been suggested as the mechanism for the alcohol-mediated elevation in steroid levels.

(e) Folate metabolism and DNA methylation

Folate deficiency is associated with different forms of cancer, of which cancer of the colon is the most common. Ethanol per se, and an underlying unhealthy lifestyle associated with high alcoholic beverage consumption, cause

folate deficiency. Several studies have shown interactions between alcohol use and polymorphisms of genes involved in folate metabolism in determining the risk for colon cancer and other cancers. The degree to which the relation between alcohol drinking, folate deficiency and cancer may be explained by the metabolism of ethanol is not known.

Other postulated modes of action of ethanol relevant to its carcinogenicity, such as tumour promotion, induction of the formation of polyunsaturated fatty acids, overproduction of mitogen-activated protein kinases, and effects on vitamin A (retinol) or insulin-like growth factors have not been rigorously established by published studies.

4.3.2 *The role of acetaldehyde in alcohol-induced carcinogenesis*

Over the past decade, epidemiological evidence of enhanced cancer risks among heterozygous carriers of the inactive ALDH enzyme has become much stronger, in particular for oesophageal cancer: practically all studies conducted in East-Asian populations who consumed alcoholic beverages show significantly increased odds ratios for carriers of the inactive ALDH allele. In addition, several studies have demonstrated associations between the polymorphism of ADH1B and upper aerodigestive tract cancers, which have been explained either by more active ADH producing more acetaldehyde or by less active ADH causing prolonged exposure to lower levels of ethanol-derived acetaldehyde. These data imply that acetaldehyde is the key compound in the development of cancers of the oesophagus and other upper aerodigestive tract cancers associated with alcoholic beverage consumption. The considerations that support this suggestion are:

1. there is an established causal relationship between alcoholic beverage consumption

- and cancers of the oesophagus, oral cavity, pharynx and larynx;
2. it is generally accepted that ethanol in alcoholic beverages is the principal ingredient that renders these beverages carcinogenic;
3. in the body, ethanol is converted by ADH and CYP2E1 to acetaldehyde, which is oxidized by ALDH to acetate;
4. the formation of acetaldehyde starts in the mouth, mediated mostly by oral bacteria, and continues along the digestive tract;
5. the main production of acetaldehyde occurs in the liver and in the gut. However, the highest levels of acetaldehyde after consumption of alcoholic beverages are found in the saliva of the oral cavity, which is in the vicinity of the target organ sites known to be susceptible to ethanol-induced cancer.
6. the upper digestive tract is also the site that is in first contact with the acetaldehyde content of the alcoholic beverages, which in turn are known to increase the salivary acetaldehyde levels;
7. acetaldehyde is a cytotoxic, genotoxic, mutagenic and clastogenic compound. It is carcinogenic in experimental animals;
8. after alcoholic beverage consumption, carriers of an inactive allele of the ALDH2 enzyme show accumulating levels of acetaldehyde in the peripheral blood, a direct consequence of their enzyme deficiency, and show increased levels of N^2 EtdG and methylhydroxypropano-dG adducts in lymphocyte DNA. The latter adducts have been shown to be formed from acetaldehyde; during DNA replication, these methylhydroxypropano-dG adducts cause mutations;
9. consumers of alcoholic beverages have a higher frequency of chromosomal aberrations, sister chromatid exchange and micronucleus formation in the peripheral lymphocytes than non-consumers. These effects may be attributable to acetaldehyde, which is a clastogen;
10. several of the observations made in ALDH2-deficient individuals have been confirmed in ALDH2-knockout mice.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of alcohol consumption. Alcohol consumption causes cancers of the oral cavity, pharynx, larynx, oesophagus, colorectum, liver (hepatocellular carcinoma) and female breast. Also, an association has been observed between alcohol consumption and cancer of the pancreas.

For cancer of the kidney and non-Hodgkin lymphoma, there is *evidence suggesting lack of carcinogenicity*.

There is *sufficient evidence* in humans for the carcinogenicity of acetaldehyde associated with the consumption of alcoholic beverages. Acetaldehyde associated with the consumption of alcoholic beverages causes cancers of the oesophagus and of upper aerodigestive tract combined.

There is *sufficient evidence* in experimental animals for the carcinogenicity of ethanol.

There is *sufficient evidence* in experimental animals for the carcinogenicity of acetaldehyde.

Alcohol consumption is *carcinogenic to humans (Group 1)*.

Ethanol in alcoholic beverages is *carcinogenic to humans (Group 1)*.

Acetaldehyde associated with the consumption of alcoholic beverages is *carcinogenic to humans (Group 1)*.

In reaching the second and third evaluations, the Working Group took the following into consideration:

- The epidemiological evidence of the carcinogenicity of alcoholic beverage consumption shows little indication that the carcinogenic effects depend on the type of alcoholic beverage, with ethanol being the common ingredient.
- Upon ingestion of alcoholic beverages, ethanol is converted into acetaldehyde, which is then oxidized to acetate.

- Ethanol and acetaldehyde are both carcinogenic in experimental animals.
- There is sufficient epidemiological evidence showing that humans who are deficient in the oxidation of acetaldehyde to acetate have a substantially increased risk for development of alcohol-related cancers, in particular of the oesophagus and the upper aerodigestive tract.

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